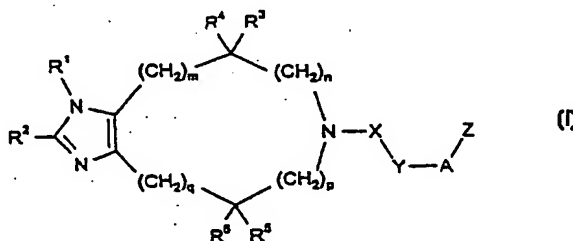




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C07D 471/04, 487/04, A61K 31/437, 31/4188		A1	(11) International Publication Number: WO 00/63208
		(43) International Publication Date: 26 October 2000 (26.10.00)	
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(22) International Filing Date: 13 April 2000 (13.04.00)			
(30) Priority Data: PA 1999 00508 16 April 1999 (16.04.99) DK PA 1999 01345 22 September 1999 (22.09.99) DK PA 2000 00042 12 January 2000 (12.01.00) DK			
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		<p>Published</p> <p><i>With international search report.</i></p> <p><i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	

(54) Title: SUBSTITUTED IMIDAZOLES, THEIR PREPARATION AND USE



(57) Abstract

A novel class of substituted imidazole compounds (I), pharmaceutical compositions comprising them and use thereof in the treatment and/or prevention of diseases and disorders related to the histamine H₃ receptor. More particularly, the compounds are useful for the treatment and/or prevention of diseases and disorders, in which an interaction with the histamine H₃ receptor is beneficial.

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TITLE

Substituted Imidazoles, their Preparation and Use

FIELD OF THE INVENTION

5 The present invention relates to novel substituted imidazoles, to the use of these compounds as medicaments, to pharmaceutical compositions comprising the compounds, and to a method of treatment employing these compounds and compositions. The present compounds show a high and selective binding affinity to the histamine H3 receptor indicating histamine H3 receptor antagonistic or agonistic activity. As a result, the compounds are useful for the treatment and/or prevention of diseases and disorders related to the histamine H3 receptor.

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BACKGROUND OF THE INVENTION

The existence of the histamine H3 receptor has been known for several years and of current interest for the development of new medicaments (see e.g. Stark, H.; Schlicker, E.; Schunack, W., *Drugs Fut.* 1996, 21, 507-520; Leurs, R.; Timmerman, H.; Vollinga, R. C., *Progress in Drug Research* 1995, 45, 107-165). Recently, the histamine H3 receptor has been cloned, cf. Lovenberg, T.W. et al, *Molecular Pharmacology*, June 1999, 55, 1101-1107. The histamine H3 receptor is a presynaptic autoreceptor located in both the central and the peripheral nervous system, the skin and in organs such as the lung, the intestine, probably the spleen and the gastrointestinal tract. The histamine H3 receptor has been demonstrated to regulate the release of histamine and also of other neurotransmitters such as serotonin and acetylcholine. A histamine H3 receptor antagonist would therefore be expected to increase the release of these neurotransmitters in the brain. A histamine H3 receptor agonist, on the contrary, leads to an inhibition of the biosynthesis of histamine and an inhibition of the release of histamine and also of other neurotransmitters such as serotonin and acetylcholine. These findings suggest that histamine H3 receptor agonists and antagonists could be important mediators of neuronal activity. Accordingly, the histamine H3 receptor is an important target for new therapeutics.

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Imidazoles similar to the compounds of the present invention have previously been prepared, and their biological properties have been investigated. Thus, WO 98/29119 relates to tetrahydroimidazopyridine farnesyl-protein inhibitors. JP 06312927 discloses tetrahydroimidazopyridine intermediates for preparing angiotensin II inhibitors. WO 5 93/17701 discloses tetrahydroimidazopyridine intermediates for preparing endothelin receptor-binding peptides. Klutchko, S., et al., *J. Heterocycl. Chem.*, 28(1), 1991, 97-108 relates to synthesis methods for the preparation of imidazole derivatives. GB 2158440 relates to antiviral compounds. Arcari, G.; Bernardi, L.; Cimaschi, R.; Falconi, G.; Luini, F.; Scarponi, U., *Arzneim. Forsch.*, 34, 11, 1984, 1467-1471, relates 10 to tetrahydroimidazopyridine intermediates for the preparation of imidazopiperidines with anti-ulcer and antisecretory activity, and GB 2028798 relates to tetrahydroimidazopyridine intermediates for the preparation of antiulcer and anticholinergic compounds. However, these references neither disclose nor suggest that the imidazoles may have a histamine H₃ receptor antagonistic or agonistic activity.

15

Furthermore, *Chem. Abstr.*, 87, 201535; Hepp, M.; Schunack, W., *Arch. Pharm. (Weinheim Ger.)*, 313, 9, 1980, 756-762; Vitali et al., *Farmaco Ed. Sci.*, 22, 1967, 821; Habermehl; Ecsy, *Heterocycles*, 5, 1976, 127; Vitali; Bertaccini, *Gazz. Chim. Ital.*, 94, 1964, 296; Emmett, J. C.; Durant, G. J.; Ganellin, C. R.; Roe, A. M.; Turner, J. L., *J. 20 Med. Chem.*, 25, 10, 1982, 1168-1174; Nagarajan, K. et al., *Indian J. Chem. Sect. B*, 15, 1977, 629-634; Casella, L.; Gullotti, M., *J. Am. Chem. Soc.*, 103, 21, 1981, 6338-6347; Piper, I. M.; MacLean, D. B.; Kvamstroem, I.; Szarek, W. A., *Can. J. Chem.*, 61, 1983, 2721-2728; Williams, R. L.; Neergaard, S., *J. Pharm. Sci.*, 71, 1, 1982, 119-120), DE 2700012, EP 589 665, EP 531 874, WO 92/18115, EP 449 521, US 5,091,390, 25 DE 33 02 125 and DE 33 02 126 disclose imidazopyridine derivatives which are stated to be useful either as intermediates or as therapeutically active substances such as angiotensin II antagonists effective to treat hypertension, peripheral kappa opioid receptor activating substances effective to treat inflammatory pain and N-myristoyl transferase inhibitors effective as anti-cancer agents. However, these references 30 neither disclose nor suggest that the imidazoles may have a histamine H₃ receptor antagonistic or agonistic activity.

Several publications disclose the preparation and use of histamine H3 agonists and antagonists. Thus, US 4,767,778 (corresponding to EP 214 058), EP 338 939, WO 93/14070, EP 531 219, EP 458 661, EP 197 840, EP 494 010, WO 91/17146, 5 WO 93/12108, WO 93/12107, WO 93/12093, US 5,578,616 (corresponding to WO 95/14007), WO 96/38142, WO 96/38141, WO 95/11894, WO 93/20061, WO 96/40126, WO 95/06037, WO 92/15567 and WO 94/17058 disclose imidazole derivatives having histamine H3 receptor agonistic or antagonistic activity. However, the structures of these imidazole derivatives are quite different from that of the present 10 compounds. Thus, none of the imidazole derivatives disclosed in these publications have a ring structure fused to the imidazole group such as is the case in the present compounds.

In view of the art's interest in histamine H3 receptor agonists and antagonists, novel 15 compounds which interact with the histamine H3 receptor would be a highly desirable contribution to the art. The present invention provides such a contribution to the art being based on the finding that a specific class of substituted imidazole compounds has a high and specific affinity to the histamine H3 receptor. Some of these substituted imidazole derivatives are novel per se thereby constituting a further aspect of the invention. 20

Due to their interaction with the histamine H3 receptor, the present compounds are useful in the treatment and/or prevention of a wide range of conditions and disorders in which an interaction with the histamine H3 receptor is beneficial. Thus, the compounds may find use eg in the treatment of diseases of the central nervous system, 25 the peripheral nervous system, the cardiovascular system, the pulmonary system, the gastrointestinal system and the endocrinological system.

DEFINITIONS

In the structural formulas given herein and throughout the present specification, the following terms have the indicated meaning:

- 5 The term "C₁₋₆-alkyl" as used herein represent a branched or straight hydrocarbon group having from 1 to 6 carbon atoms. Typical C₁₋₆-alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, isopentyl, hexyl, isohexyl and the like.
- 10 The term "C₂₋₈-alkenyl" as used herein represents a branched or straight hydrocarbon group having from 2 to 8 carbon atoms and at least one double bond. Examples of such groups include, but are not limited to, vinyl, 1-propenyl, 2-propenyl, allyl, iso-propenyl, 1,3-butadienyl, 1-butenyl, 2-butenyl, 1-pentenyl, 2-pentenyl, 1-hexenyl, 2-hexenyl, 1-heptenyl, 2-heptenyl, 1-octenyl, 2-octenyl and the like. In a similar way
- 15 the term "C₂₋₆-alkenyl" represents a branched or straight hydrocarbon group having from 2 to 6 carbon atoms and at least one double bond.

The term "C₂₋₈-alkynyl" as used herein represents a branched or straight hydrocarbon group having from 2 to 8 carbon atoms and at least one triple bond. Examples of

20 such groups include, but are not limited to, 1-propynyl, 2-propynyl, 1-butylnyl, 2-butylnyl, 1-pentylnyl, 2-pentylnyl, 1-hexylnyl, 2-hexylnyl, 1-heptynyl, 2-heptynyl, 1-octynyl, 2-octynyl and the like. In a similar way the term "C₂₋₆-alkynyl" represents a branched or straight hydrocarbon group having from 2 to 6 carbon atoms and at least one triple bond.

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The term "C₁₋₆-alkoxy" as used herein, alone or in combination, refers to the radical -O-C₁₋₆-alkyl where C₁₋₆-alkyl is as defined above. Representative examples are methoxy, ethoxy, n-propoxy, isopropoxy, butoxy, *sec*-butoxy, *tert*-butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy and the like.

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The term "C₁₋₈-alkylthio" as used herein, alone or in combination, refers to the radical -S-C₁₋₈-alkyl where C₁₋₈-alkyl is as defined above. Representative examples are methylthio, ethylthio, isopropylthio, propylthio, butylthio, pentylthio and the like.

- 5 The term "C₃₋₁₅-cycloalkyl" as used herein represents a carbocyclic group having from 3 to 15 carbon atoms such as from 3 to 8 carbon atoms. Representative examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl and the like. In the same way the term "C₃₋₈-cycloalkyl" represents a carbocyclic group having from 3 to 8 carbon atoms

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The term "C₃₋₁₅-cycloalkenyl" as used herein represents a carbocyclic group having from 3 to 15 carbon atoms such as from 3 to 8 carbon atoms and at least one double bond. Representative examples are cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclononenyl, cyclodecenyl and the like.

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The term "C₃₋₁₅-cycloalkynyl" as used herein represents a carbocyclic group having from 3 to 15 carbon atoms such as from 3 to 8 carbon atoms and at least one triple bond. Representative examples are cyclopropynyl, cyclobutynyl, cyclopentynyl, cyclohexynyl, cycloheptynyl, cyclooctynyl, cyclononyl, cyclodecynyl and the like.

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The term "aryl" as used herein is intended to include carbocyclic aromatic ring systems such as phenyl, naphthyl (1-naphthyl or 2-naphthyl), anthracenyl (1-anthracenyl, 2-anthracenyl, 3-anthracenyl), phenanthrenyl, fluorenyl, indenyl and the like. Aryl is also intended to include the partially hydrogenated derivatives of the carbocyclic systems enumerated above. Non-limiting examples of such partially hydrogenated derivatives are 1-(1,2,3,4-tetrahydronaphthyl) and 2-(1,2,3,4-tetrahydronaphthyl).

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The term "aroyl" as used herein refers to the radical -CO-aryl where aryl is as defined above. Non-limiting examples are benzoyl, naphthoyl, anthracenoyl, phenanthrenoyl, fluorenyl, indenoyl and the like.

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The term "aryloxy" as used herein refers to the radical -O-aryl where aryl is as defined above. Non-limiting examples are phenoxy, naphthoxy, anthracenyloxy, phenantrenyloxy, fluorenyloxy, indenylloxy and the like.

- 5 The term "arylthio" as used herein refers to the radical -S-aryl where aryl is as defined above. Non-limiting examples are phenylthio, naphthylthio, phenanthrenylthio, fluorenylthio, indenylthio and the like.

- 10 The term "arylamino" as used herein refers to the radical -NH-aryl where aryl is as defined above. Non-limiting examples are phenylamino, naphthylamino, phenanthrenylamino, fluorenylamino, indenylamino and the like.

- 15 The term "arylsulfonyl" as used herein refers to the radical -S(=O)₂-aryl where aryl is as defined above. Non-limiting examples are phenylsulfonyl, naphthylsulfonyl, phenanthrenylsulfonyl, fluorenylsulfonyl, indenylsulfonyl and the like.

- The term "heteroaryl" as used herein is intended to include heterocyclic aromatic ring systems containing one or more heteroatoms selected from nitrogen, oxygen and sulfur such as furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, pyran, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, thiadiazinyl, indolyl, isoindolyl, benzofuryl, benzothienyl, benzothiophenyl (thianaphthenyl), indazolyl, benzimidazolyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, purinyl, quinazolinyl, quinoliziny, quinolinyl, isoquinolinyl, quinoxaliny, naphthyridinyl, pteridinyl, carbazolyl, azepinyl, diazepinyl, acridinyl and the like. Heteroaryl is also intended to include the partially or fully hydrogenated derivatives of the heterocyclic systems enumerated above. Non-limiting examples of such partially or fully hydrogenated derivatives are pyrrolinyl, pyrazolinyl, indolinyl, pyrrolidinyl, piperidinyl,
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piperazinyl, azepinyl, diazepinyl, morpholinyl, thiomorpholinyl, oxazolidinyl, oxazoliny, oxazepinyl, aziridinyl and tetrahydrofuranyl.

The term "heteroaroyle" as used herein refers to the radical -CO-heteroaryl where
5 heteroaryl is as defined above. Non-limiting examples are furyl, thienylcarbonyl, pyridoyl, oxazolylcarbonyl, benzofurylcarbonyl, benzimidazolylcarbonyl, pyrrolinylcarbonyl, azepinylcarbonyl and the like.

The term "heteroaryloxy" as used herein refers to the radical -O-heteroaryl where
10 heteroaryl is as defined above. Non-limiting examples are furyloxy, thienyloxy, pyridyloxy, oxazolyloxy, benzofuryloxy, benzimidazolylloxy, pyrrolinyloxy, azepinyloxy and the like.

The term "heteroarylamino" as used herein refers to the radical -NH-heteroaryl where
15 heteroaryl is as defined above. Non-limiting examples are furylamino, thienylamino, pyridylamino, oxazolylamino, benzofurylamino, benzimidazolylamino, pyrrolinylamino, azepinylamino and the like.

The term "heteroarylthio" as used herein refers to the radical -S-heteroaryl where
20 heteroaryl is as defined above. Non-limiting examples are furylthio, thienylthio, pyridylthio, oxazolylthio, benzofurylthio, benzimidazolylthio, pyrrolinylthio, azepinylthio and the like.

The term "heteroarylsulfonyl" as used herein refers to the radical -S(=O)₂-heteroaryl
25 where heteroaryl is as defined above. Non-limiting examples are furylsulfonyl, thienylsulfonyl, pyridylsulfonyl, oxazolylsulfonyl, benzofurylsulfonyl, benzimidazolylsulfonyl, pyrrolinylsulfonyl, azepinylsulfonyl and the like.

The term "acylamino" as used herein represents a radical of the form -N(L)-C(=O)-G
30 where G and L independently represent hydrogen, C₁₋₆-alkyl, aryl or heteroaryl as

defined above. Non-limiting examples are acetylamino, propanoylamino, butyrylamino, pentanoylamino, benzoylamino, furoylamino, pyridoylamino and the like.

The term "sulfonylamino" as used herein represents a radical of the form

5 -N(L)-S(=O)₂-G where G and L independently represent hydrogen, C₁₋₈-alkyl, aryl or heteroaryl as defined above. Non-limiting examples are methanesulfonylamino, propanesulfonylamino, benzenesulfonylamino, *N*-methyl-*N*-(benzenesulfonyl)amino, 4-methylbenzenesulfonylamino *N*-butyl-*N*-(4-methylbenzenesulfonyl)amino, 2-thienylsulfonylamino and the like.

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The term "halogen" means fluorine, chlorine, bromine or iodine.

As used herein, the phrase "3 to 8 membered, saturated or unsaturated, carbocyclic or heterocyclic ring" is intended to include carbocyclic rings which are saturated or

15 contain one or more double bonds as well as heterocyclic rings containing one or more heteroatoms selected from nitrogen, oxygen or sulfur which are saturated or contain one or more double bonds.

Certain of the above defined terms may occur more than once in the structural

20 formulas, and upon such occurrence each term shall be defined independently of the other.

The term "optionally substituted" as used herein means that the groups in question are either unsubstituted or substituted with one or more of the substituents specified.

25 When the groups in question are substituted with more than one substituent the substituents may be the same or different.

As used herein, the phrase "a functional group which can be converted to hydrogen *in vivo*" is intended to include any group which upon administering the present compounds to the subjects in need thereof can be converted to hydrogen e.g. enzymatically or by the acidic environment in the stomach. Non-limiting examples of such

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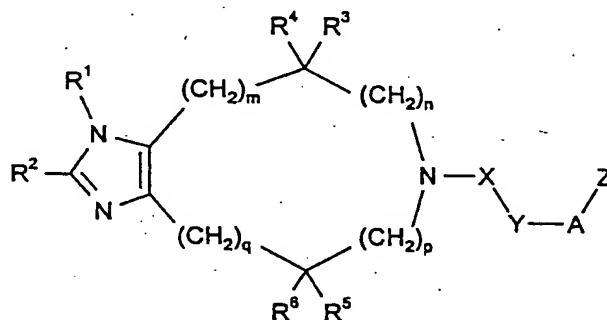
groups are acyl, carbamoyl, monoalkylated carbamoyl, dialkylated carbamoyl, alkoxy carbonyl, alkoxyalkyl groups and the like such as C₁₋₈-alkanoyl, aroyl, C₁₋₈-alkylcarbamoyl, di-C₁₋₈-alkylcarbamoyl, C₁₋₈-alkoxy carbonyl and C₁₋₈-alkoxy-C₁₋₈-alkyl.

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As used herein, the phrase "diseases and disorders related to the histamine H3 receptor" is intended to include any disease or disorder in which an effect, either antagonistic or agonistic, on the histamine H3 receptor is beneficial.

10 DESCRIPTION OF THE INVENTION

The present invention relates to novel, substituted imidazoles of the general formula I



15 wherein

R¹ is hydrogen or a functional group, which can be converted to hydrogen *in vivo*;

R² is hydrogen, C₁₋₈-alkyl, halogen, cyano, trifluoromethyl, trifluoromethoxy, hydroxy
20 or -NR⁷R⁸,

wherein R⁷ and R⁸ independently are

hydrogen,

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C₁₋₈-alkyl optionally substituted with

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroaryl-amino or C₃₋₈-cycloalkyl, which are optionally substituted with

C₁₋₈-alkyl, C₁₋₈-alkoxy, C₁₋₈-alkylthio, hydroxy, amino, C₁₋₈-alkylamino, di(C₁₋₈-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroaryl-amino,

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl or heteroarylsulfonyl, which are optionally substituted with

C₁₋₈-alkyl, C₁₋₈-alkoxy, C₁₋₈-alkylthio, hydroxy, amino, C₁₋₈-alkylamino, di(C₁₋₈-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroaryl-amino,

C₁₋₈-alkylsulfonyl optionally substituted with

C₃₋₈-cycloalkyl, C₁₋₈-alkoxy, C₁₋₈-alkylthio, hydroxy, amino, C₁₋₈-alkylamino, di(C₁₋₈-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroaryl-amino, or

R⁷ and R⁸, together with the nitrogen atom to which they are connected, form a 3 to 8 membered, saturated or unsaturated, heterocyclic ring optionally containing one or more further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally substituted with C₁₋₈-alkyl, C₁₋₈-alkoxy, C₁₋₈-alkylthio, hydroxy, amino, C₁₋₈-alkylamino, di(C₁₋₈-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroaryl-amino;

R³, R⁴, R⁵ and R⁶ independently are

hydrogen, carboxy, C₁₋₈-alkoxycarbonyl, cyano, trifluoromethyl, halogen,

C₃₋₈-cycloalkyl optionally substituted with

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino,
di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, het-
eroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

C₁₋₆-alkyl, C₂₋₆-alkenyl or C₂₋₆-alkynyl, which are optionally substituted with

C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, cyano, halogen, trifluoromethyl, trifluoro-
methoxy, carboxy, C₁₋₆-alkoxycarbonyl,

C₃₋₈-cycloalkyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or
heteroarylamino, which are optionally substituted with

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino,
di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl,
heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroarylamino or
-CO-NR⁹R¹⁰,

aryl optionally substituted with

halogen, cyano, nitro, C₁₋₆-alkyl, C₁₋₆-alkoxy, hydroxy, trifluoromethyl, trifluoro-
methoxy, aryl, heteroaryl, aryloxy, aroyl, heteroaroyl, arylsulfonyl, arylamino,
heteroarylamino or -CO-NR⁹R¹⁰,

-CO-NR⁹R¹⁰,

wherein R⁹ and R¹⁰ independently are

hydrogen,

C₁₋₆-alkyl optionally substituted with

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroaryl-
amino or C₃₋₈-cycloalkyl, which are optionally substituted with

C₁₋₈-alkyl, C₁₋₈-alkoxy, C₁₋₈-alkylthio, hydroxy, amino, C₁₋₈-alkylamino, di(C₁₋₈-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

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aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl or heteroarylsulfonyl, which are optionally substituted with

C₁₋₈-alkyl, C₁₋₈-alkoxy, C₁₋₈-alkylthio, hydroxy, amino, C₁₋₈-alkylamino, di(C₁₋₈-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

10

C₁₋₈-alkylsulfonyl optionally substituted with

C₃₋₈-cycloalkyl, C₁₋₈-alkoxy, C₁₋₈-alkylthio, hydroxy, amino, C₁₋₈-alkylamino, di(C₁₋₈-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino, or

15

R⁹ and R¹⁰, together with the nitrogen atom to which they are connected, form a 3 to 8 membered, saturated or unsaturated, heterocyclic ring optionally containing one or more further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally substituted with C₁₋₈-alkyl, C₁₋₈-alkoxy, C₁₋₈-alkylthio, hydroxy, amino, C₁₋₈-alkylamino, di(C₁₋₈-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino, or

20

25

R³ and R⁴, together with the carbon atom to which they are connected, and/or R⁵ and R⁶ together with the carbon atom to which they are connected, form a 3 to 8 membered, saturated or unsaturated, carbocyclic or heterocyclic ring optionally substituted with C₁₋₈-alkyl, C₁₋₈-alkoxy, C₁₋₈-alkylthio, hydroxy, amino, C₁₋₈-alkylamino, di(C₁₋₈-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

30

m, n, p and q independently are 0, 1 or 2;

X is a valence bond, $-\text{CH}_2-$, $-\text{C}(=\text{O})-$, $-\text{C}(=\text{S})-$, $-\text{S}(=\text{O})-$, $-\text{S}(=\text{O})_2-$, $-\text{C}(=\text{N}-\text{CN})-$,
5 $-\text{C}(=\text{CH}-\text{NO}_2)-$, $-\text{C}[\text{C}(\text{CN})_2]-$, $-\text{C}(=\text{CH}-\text{CN})-$, $-\text{C}(=\text{NR}^{11})-$ or $-\text{C}(=\text{N}-\text{S}(=\text{O})_2\text{R}^{11a})-$,

wherein R^{11} is

hydrogen,

10 C_{1-6} -alkyl optionally substituted with

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroaryl-
amino or C_{3-8} -cycloalkyl, which are optionally substituted with

15 C_{1-6} -alkyl, C_{1-6} -alkoxy, C_{1-6} -alkylthio, hydroxy, amino, C_{1-6} -alkylamino,
di(C_{1-6} -alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy,
aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroaryl-
amino,

20 aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl or heteroarylsulfonyl, which are
optionally substituted with

C_{1-6} -alkyl, C_{1-6} -alkoxy, C_{1-6} -alkylthio, hydroxy, amino, C_{1-6} -alkylamino,
di(C_{1-6} -alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl,
heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroaryl-
amino,

25 C_{1-6} -alkylsulfonyl optionally substituted with

C_{3-8} -cycloalkyl, C_{1-6} -alkoxy, C_{1-6} -alkylthio, hydroxy, amino, C_{1-6} -alkylamino,
di(C_{1-6} -alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl,
heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroaryl-
amino;

30 R^{11a} is

C₁₋₆-alkyl optionally substituted with

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroaryl-amino or C₃₋₈-cycloalkyl, which are optionally substituted with

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino,
di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy,
aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or het-
eroarylamino,

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl or heteroarylsulfonyl, which are
optionally substituted with

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino,
di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl,
heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

Y is a valence bond, -O- or -N(R¹²)-,

wherein R¹² is

hydrogen,

C₁₋₆-alkyl optionally substituted with

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroaryl-amino or C₃₋₈-cycloalkyl, which are optionally substituted with

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino,
di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy,
aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or het-
eroarylamino,

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl or heteroarylsulfonyl, which are
optionally substituted with

C₁₋₈-alkyl, C₁₋₈-alkoxy, C₁₋₈-alkylthio, hydroxy, amino, C₁₋₈-alkylamino, di(C₁₋₈-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

5 C₁₋₈-alkylsulfonyl optionally substituted with C₃₋₈-cycloalkyl, C₁₋₈-alkoxy, C₁₋₈-alkylthio, hydroxy, amino, C₁₋₈-alkylamino, di(C₁₋₈-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

10 A is a valence bond, C₁₋₈-alkylene, C₂₋₈-alkenylene, C₂₋₈-alkynylene, C₃₋₈-cycloalkylene or phenylene, or

when Y is -N(R¹²)-, A, together with R¹² and the nitrogen atom to which they are connected, may form a 3 to 8 membered, saturated or unsaturated, heterocyclic
15 ring system optionally containing one or more further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally substituted with C₁₋₈-alkyl, C₁₋₈-alkoxy, C₁₋₈-alkylthio, hydroxy, amino, C₁₋₈-alkylamino, di(C₁₋₈-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aryl-C₁₋₈-alkyl, heteroaryl-C₁₋₈-alkyl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino; and
20

Z is -R¹³, -OR¹³, -SR¹³, -NR¹³R¹⁴, -CHR¹³R¹⁴, -CR¹³R¹⁴R¹⁵ or =CR¹³R¹⁴,

wherein R¹³, R¹⁴ and R¹⁵ independently are

25

hydrogen,

C₁₋₈-alkyl, C₂₋₈-alkenyl or C₂₋₈-alkynyl, which are optionally substituted with aryl, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, C₁₋₈-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, heteroaryl or C₃₋₈-cycloalkyl, which are optionally substituted with
30

C₁₋₈-alkyl, C₁₋₈-alkoxy, C₁₋₈-alkylthio, aryl-C₁₋₈-alkyl, heteroaryl-C₁₋₈-alkyl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C₁₋₈-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, hydroxy, amino, C₁₋₈-alkylamino, di(C₁₋₈-alkyl)amino, halogen, cyano, trifluoromethoxy or trifluoromethyl,

aryl, C₃₋₁₅-cycloalkyl, C₃₋₁₅-cycloalkenyl, C₃₋₁₅-cycloalkynyl, aroyl or heteroaryl, which are optionally substituted with

aryl-C₁₋₈-alkyl, heteroaryl-C₁₋₈-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C₁₋₈-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C₁₋₈-alkyl, C₁₋₈-alkoxy, C₁₋₈-alkylthio, C₃₋₈-cycloalkanecarbonyl, hydroxy, amino, C₁₋₈-alkylamino, di(C₁₋₈-alkyl)amino, halogen, cyano, trifluoromethoxy or trifluoromethyl, where

R¹³ and R¹⁴ or R¹³, R¹⁴ and R¹⁵, when they do not represent hydrogen, may be joined by one or more bridging linkers such as a valence bond, C₁₋₄-alkylene, C₂₋₄-alkenylene, -O-, -S-, -N(R¹⁶)-, -C(=O)-, -S(=O)-, -S(=O)₂-, -C(R¹⁶R¹⁷)-, phenylene, biphenylene, -O-C₁₋₄-alkylene, -S-C₁₋₄-alkylene, -N(R¹⁶)-C₁₋₄-alkylene, -N=C₁₋₄-alkylene, -O-C₂₋₄-alkenylene, -S-C₂₋₄-alkenylene or -N(R¹⁶)-C₂₋₄-alkenylene, to form a mono-, bi- or polycyclic ring system,

wherein R¹⁶ and R¹⁷ independently are

hydrogen,

C₁₋₈-alkyl optionally substituted with

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroarylamino or C₃₋₈-cycloalkyl, which are optionally substituted with

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkyl-amino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

5

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl or heteroarylsulfonyl, which are optionally substituted with

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

10

C₁₋₆-alkylsulfonyl optionally substituted with

C₃₋₈-cycloalkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino, or

15

R¹⁶ and R¹⁷, together with the nitrogen atom to which they are connected, form a 3 to 8 membered, saturated or unsaturated, heterocyclic ring optionally containing one or more further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally substituted with C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

20

25

with the provisos that

when X is -CS-, R¹ = R² = R⁵ = R⁶ = hydrogen, m = n = p = 0 and q = 1, the group -Y-A-Z must not start with the radical -NH-;

30

when the group -X-Y-A-Z starts with the radical -CH₂-, R¹ = R² = R⁶ = hydrogen, m = n = p = 0 and q = 1, R⁵ must not be carboxy or aminocarbonyl;

5 when X is -CO-, the group -Y-A-Z starts with the radical -NH-, R¹ = R² = R⁶ = hydrogen, m = n = p = 0 and q = 1, the remainder of the group -Y-A-Z must not be hydrogen, unsubstituted or C₁₋₆-alkoxy substituted phenyl, unsubstituted C₃₋₈-cycloalkyl or unsubstituted C₁₋₆-alkyl;

10 when X is -CO-, Y is -O-, A is -CH₂-, Z is phenyl, R¹ = R² = R³ = R⁴ = R⁶ = hydrogen, m = n = p = 0 and q = 1, R⁵ must not be carboxy, aminocarbonyl or 4-phenyl-piperazin-1-ylcarbonyl;

15 when X is -CO-, Y is -O-, A is -CH₂-, Z is phenyl, R¹ = R³ = R⁴ = R⁶ = hydrogen, R² = butyl, m = n = p = 0 and q = 1, R⁵ must not be methoxycarbonyl;

when X is -CO-, Y is -O-, A is -CH₂-, Z is phenyl, R¹ = R² = R⁴ = R⁵ = R⁶ = hydrogen, m = n = p = 0 and q = 1, R³ must not be hydrogen, ethyl, isopropyl or phenyl;

20 when X is -CO-, Y is -O-, A is a valence bond, Z is *tert*-butyl, R¹ = R² = R³ = R⁴ = R⁶ = hydrogen, m = n = p = 0 and q = 1, R⁵ must not be carboxy;

when X is -CO-, Y is -O-, A is a valence bond, Z is *tert*-butyl, R¹ = R² = R⁴ = R⁵ = R⁶ = hydrogen, m = n = p = 0 and q = 1, R³ must not be 4-cyanophenyl;

25 when X is -CO-, the group -Y-A-Z starts with the radical -O-, R¹ = R² = R⁶ = hydrogen, m = n = p = 0 and q = 1, R⁵ must not be carboxy, aminocarbonyl or hydrogen;

30 when -X is -CO-, the group -Y-A-Z starts with the radical -CH<, R¹ = R² = R³ = R⁴ = R⁶ = hydrogen, m = n = p = 0 and q = 1, R⁵ must not be hydroxymethyl, C₁₋₆-alkoxy-carbonyl or carboxy; and

when X is -CO-, the group -Y-A-Z is 4-methoxyphenyl, $R^1 = R^2 = R^3 = R^4 = R^6 =$ hydrogen, $m = n = p = 0$ and $q = 1$, R^5 must not be carboxy;

as well as any optical or geometric isomer or tautomeric form thereof including mix-
5 tures of these or a pharmaceutically acceptable salt thereof.

Preferably, $R^1 = R^2 =$ hydrogen.

In a preferred embodiment $m = n = p = 0$, and $q = 1$.

10

In another preferred embodiment $n = p = 0$, and $m = q = 1$.

Preferably, X is a valence bond, -C(=O)-, -S(=O)₂-, -C(=N-CN)-, -C(=CH-NO₂)- or
-C(=N-S(=O)₂R^{11a})-, wherein R^{11a} is as defined for formula I above.

15

More preferably, X is preferably -C(=O)-.

Preferably, A is a valence bond, C₁₋₈-alkylene, C₂₋₈-alkenylene or C₂₋₈-alkynylene.

20 More preferably, A is a valence bond or C₁₋₈-alkylene, such as methylene, ethylene or propylene.

Preferably, Z is -R¹³, -NR¹³R¹⁴, -CHR¹³R¹⁴ or -CR¹³R¹⁴R¹⁵, wherein R¹³, R¹⁴ and R¹⁵ are
as defined for formula I above.

25

In a preferred embodiment Z is -R¹³, wherein R¹³ is as defined for formula I above.

Of these Z is preferably C₁₋₈-alkyl, aryl, C₃₋₁₅-cycloalkyl, C₃₋₁₅-cycloalkenyl, aroyl or
heteroaryl, which are optionally substituted as defined for formula I above.

30

More preferably, Z is C₁₋₆-alkyl, phenyl, naphthyl, thienyl, cyclopentyl, cyclohexyl, cyclohexenyl, oxazolyl, indanyl, isoquinolyl, benzoyl or tetrahydronaphthyl, which are optionally substituted for formula I above.

- 5 Even more preferably, Z is phenyl or cyclohexyl, which are optionally substituted as defined for formula I above.

Z may be unsubstituted or substituted with one to three substituents selected from C₁₋₆-alkyl, C₁₋₆-alkoxy, halogen, phenyl, di(C₁₋₆-alkyl)amino, C₃₋₈-cyclopropane-
10 carbonyl, trifluoromethoxy and trifluoromethyl.

In another preferred embodiment Z is -NR¹³R¹⁴, in which R¹³ and R¹⁴ are both phenyl, which phenyl groups are joined with a C₁₋₄-alkylene group to form a tricyclic ring system, such as 10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl.

15

In yet another preferred embodiment Z is -CHR¹³R¹⁴, in which R¹³ is C₁₋₆-alkyl or phenyl and R¹⁴ is phenyl, or R¹³ and R¹⁴ are both C₁₋₆-alkyl, which are joined with C₁₋₄-alkylene linkers to form a polycarbocyclic ring system, such as bicyclo[2.2.1]hept-2-yl.

20

In a further preferred embodiment Z is -CR¹³R¹⁴R¹⁵, in which R¹³, R¹⁴ and R¹⁵ are C₁₋₆-alkyl, which are joined with C₁₋₄-alkylene linkers to form a polycarbocyclic ring system, such as adamantyl.

- 25 Preferably, R³ and R⁴ are independently

hydrogen;

C₃₋₈-cycloalkyl optionally substituted with C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy,
30 amino, C₁₋₆-alkylamino, di(C₁₋₆-alkylamino), halogen, cyano, trifluoromethyl, trifluoro-

methoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

C₁₋₆-alkyl optionally substituted with

- 5 C₃₋₈-cycloalkyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino which are optionally substituted with

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkylamino), halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

10

aryl optionally substituted with

halogen, cyano, nitro, C₁₋₆-alkyl, C₁₋₆-alkoxy, hydroxy, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aryloxy, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroarylamino or -CO-NR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined in claim 1,

15

or

R³ and R⁴, together with the carbon atom to which they are connected, form a C₃₋₈-cycloalkyl ring optionally substituted with C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkylamino), halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino.

20

More preferably, R³ and R⁴ are both hydrogen or are both C₁₋₆-alkyl, or R³ and R⁴, together with the carbon atom to which they are connected, form a C₃₋₈-cycloalkyl ring, or one of R³ and R⁴ is hydrogen while the other is C₃₋₈-cycloalkyl substituted C₁₋₆-alkyl.

25

Preferably, R⁵ and R⁶ are both hydrogen.

30 In a preferred embodiment R³, R⁴, R⁵ and R⁶ are hydrogen.

In a preferred embodiment $m = n = p = 0$, and $q = 1$, or $n = p = 0$, and $m = q = 1$; $R^1 = R^2 = \text{hydrogen}$; R^3, R^4, R^5 and R^6 are hydrogen; X is $-\text{C}(=\text{O})-$; Y is $-\text{N}(\text{R}^{12})-$, wherein R^{12} and A, together with the nitrogen atom to which they are connected, form a 3 to 8 membered, saturated or unsaturated, heterocyclic ring system optionally containing one or more further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally substituted with C_{1-6} -alkyl, C_{1-6} -alkoxy, C_{1-6} -alkylthio, hydroxy, amino, C_{1-6} -alkylamino, di(C_{1-6} -alkylamino), halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aryl- C_{1-6} -alkyl, heteroaryl- C_{1-6} -alkyl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino; and Z is $-\text{R}^{13}$, wherein R^{13} is hydrogen.

In another preferred embodiment $m = n = p = 0$, and $q = 1$, or $n = p = 0$, and $m = q = 1$; $R^1 = R^2 = \text{hydrogen}$; R^3, R^4, R^5 and R^6 are hydrogen; X is $-\text{C}(=\text{N}-\text{CN})-$, $-\text{C}(=\text{CH}-\text{NO}_2)-$ or $-\text{C}(=\text{N}-\text{S}(=\text{O})_2\text{R}^{11a})-$, wherein R^{11a} is C_{1-6} -alkyl or phenyl substituted with C_{1-6} -alkyl; Y is $-\text{NH}-$; A is C_{1-8} -alkylene; and Z is $-\text{R}^{13}$, wherein R^{13} is C_{1-6} -alkyl, aryl, C_{3-15} -cycloalkyl, C_{3-15} -cycloalkenyl, aroyl or heteroaryl, which are optionally substituted as defined for formula I above.

In yet another preferred embodiment $m = n = p = 0$, and $q = 1$, or $n = p = 0$, and $m = q = 1$; $R^1 = R^2 = \text{hydrogen}$; R^3, R^4, R^5 and R^6 are hydrogen; X is $-\text{S}(=\text{O})_2-$; Y is a valence bond; A is a valence bond or C_{1-8} -alkylene; and Z is $-\text{R}^{13}$, wherein R^{13} is C_{1-6} -alkyl, aryl, C_{3-15} -cycloalkyl, C_{3-15} -cycloalkenyl, aroyl or heteroaryl, which are optionally substituted as defined for formula I above.

In still another preferred embodiment $m = n = p = 0$, and $q = 1$, or $n = p = 0$, and $m = q = 1$; $R^1 = R^2 = \text{hydrogen}$; R^3, R^4, R^5 and R^6 are hydrogen; X is $-\text{C}(=\text{O})-$; Y is $-\text{N}(\text{R}^{12})-$, wherein R^{12} is hydrogen or C_{1-6} -alkyl; A is a valence bond or C_{1-8} -alkylene; and Z is $-\text{R}^{13}$, wherein R^{13} is C_{1-6} -alkyl, aryl, C_{3-15} -cycloalkyl, C_{3-15} -cycloalkenyl, aroyl or heteroaryl, which are optionally substituted as defined for formula I above.

In a further preferred embodiment $m = n = p = 0$, and $q = 1$, or $n = p = 0$, and $m = q = 1$; $R^1 = R^2 = \text{hydrogen}$; R^3, R^4, R^5 and R^6 are hydrogen; X is $-\text{C}(=\text{O})-$; Y is $-\text{O}-$; A is a

valence bond or C_{1-8} -alkylene; and Z is $-R^{13}$, wherein R^{13} is C_{1-8} -alkyl, aryl, C_{3-15} -cycloalkyl, C_{3-15} -cycloalkenyl, aroyl or heteroaryl, which are optionally substituted as defined for formula I above.

- 5 In yet a further preferred embodiment $m = n = p = 0$, and $q = 1$, or $n = p = 0$, and $m = q = 1$; $R^1 = R^2 = \text{hydrogen}$; R^3, R^4, R^5 and R^6 are hydrogen; X is $-\text{C}(=\text{O})-$; Y is a valence bond; A is a valence bond or C_{1-8} -alkylene; and Z is $-R^{13}$, wherein R^{13} is C_{1-8} -alkyl, aryl, C_{3-15} -cycloalkyl, C_{3-15} -cycloalkenyl, aroyl or heteroaryl, which are optionally substituted as defined for formula I above.

10

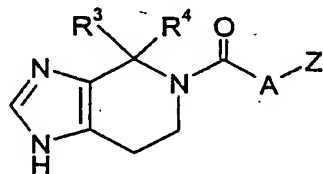
More preferably, Z is C_{1-8} -alkyl, phenyl, naphthyl, thienyl, cyclopentyl, cyclohexyl, cyclohexenyl, oxazolyl, indanyl, isoquinolyl, benzoyl or tetrahydronaphthyl, which are optionally substituted as defined for formula I above.

- 15 Even more preferably, Z is phenyl or cyclohexyl which are optionally substituted as defined for formula I above.

Z may be unsubstituted or substituted with one to three substituents selected from C_{1-8} -alkyl, C_{1-8} -alkoxy, halogen, phenyl, $\text{di}(C_{1-8}\text{-alkyl})\text{amino}$, C_{3-8} -cyclopropane-carbonyl, trifluoromethoxy and trifluoromethyl.

20

Specific examples of the above-preferred embodiments of the present invention are the following compounds:



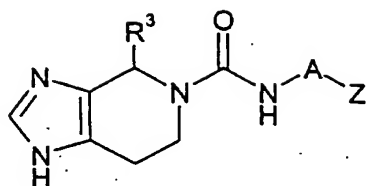
25

wherein

R ³	R ⁴	A	Z
H	H	methylene	cyclohexyl
H	H	ethylene	4-fluorobenzoyl
H	H	bond	cyclohexyl
H	H	pentylene	benzoyl
H	H	ethylene	cyclohexyl
H	H	pentylene	phenyl
H	H	butylene	cyclohexyl
H	H	bond	methyl
H	H	methylene	diphenylmethyl
H	H	ethylene	10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl
CH ₃	CH ₃	ethylene	cyclohexyl
H	4-isopropylphenyl	ethylene	4-fluorophenyl
CH ₃	CH ₂ CH ₃	ethylene	cyclohexyl
spiro-	-(CH ₂) ₃ -	ethylene	cyclohexyl
H	H	bond	3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl
H	H	methylene	<i>tert</i> -butyl
H	H	ethynylene	phenyl
H	H	ethenylene	4- <i>tert</i> -butylphenyl
H	H	methylene	bicyclo[2.2.1]hept-2-yl
H	H	bond	4-pentylphenyl
H	H	bond	4-trifluoromethoxyphenyl
H	H	bond	4-trifluoromethylphenyl
H	H	bond	4-isobutylphenyl
H	H	bond	4-chlorophenyl

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

- 5 Specific examples of the above-preferred embodiments of the present invention are the following compounds:



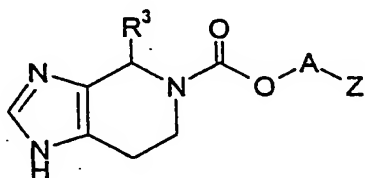
wherein

5

R ³	A	Z
H	-(CH ₂) ₂ -	2-thienyl
H	bond	3,5-dimethyl-1,2-oxazol-4-yl
H	-CH(CH ₃)-	1-naphthyl
H	bond	2-phenylcyclopropyl
H	bond	1-(4-bromophenyl)ethyl
H	bond	2-(trifluoromethyl)phenyl
H	ethylene	phenyl
H	bond	4-(trifluoromethyl)phenyl
H	bond	3-cyanophenyl
H	bond	4-cyanophenyl
H	bond	n-octyl
H	methylene	2,4-dichlorophenyl
2-cyclohexylethyl	bond	ethyl
2-cyclohexylethyl	methylene	2,4-dichlorophenyl

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

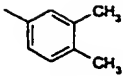

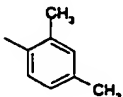


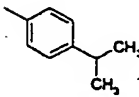
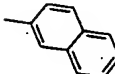
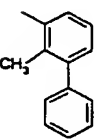
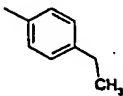



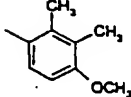



Specific examples of the above-preferred embodiments of the present invention are the following compounds:

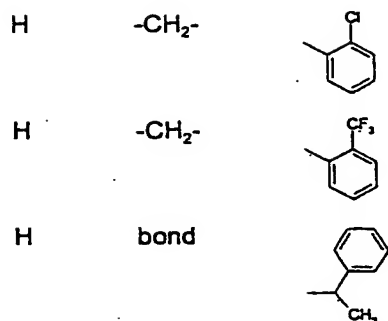


5

wherein

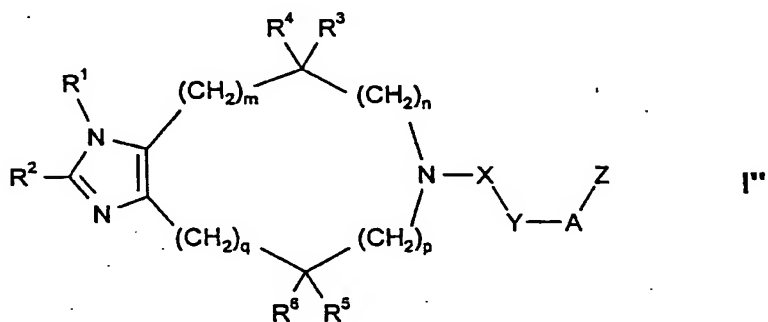
R ³	A	Z
H	-CH ₂ -	
H	-CH ₂ -	
H	-CH ₂ -	
H	-CH ₂ -	
H	-CH ₂ -	
H	-CH ₂ -	
H	-CH ₂ -	
H	-CH ₂ -	
H	-(CH ₂) ₂ -	
H	-(CH ₂) ₂ -	
H	-CH ₂ -	

H	-CH ₂ -	
H	-CH ₂ -	
H	-CH ₂ -	
H	-(CH ₂) ₂ -	
H	-CH ₂ -	
H	-CH ₂ -	
H	-CH ₂ -	
H	-CH ₂ -	
H	-CH ₂ -	
H	-CH ₂ -	
H	-(CH ₂) ₂ -	
H	-(CH ₂) ₂ -	
H	-CH ₂ -	
-CF ₃	-CH ₂ -	
H	-(CH ₂) ₂ -	
H	-CH ₂ -	



as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

- 5 In a further aspect the invention relates to novel, substituted imidazoles of the general formula I''



- 10 wherein

R¹ is hydrogen or a functional group which can be converted to hydrogen *in vivo*;

R² is hydrogen, C₁₋₆-alkyl, halogen, cyano, trifluoromethyl, hydroxy or -NR⁷R⁸,

15

wherein R⁷ and R⁸ independently are

hydrogen,

C₁₋₆-alkyl optionally substituted with

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroaryl-
amino or C₃₋₈-cycloalkyl, which are optionally substituted with

5 C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, halogen, cyano,
trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, aryl-
amino or heteroarylamino,

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl or heteroarylsulfonyl, which are
optionally substituted with

10 C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, halogen, cyano,
trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino
or heteroarylamino,

C₁₋₆-alkylsulfonyl optionally substituted with

15 C₃₋₈-cycloalkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, halogen, cyano,
trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino
or heteroarylamino, or

20 R⁷ and R⁸, together with the nitrogen atom to which they are connected, form a
3 to 8 membered, saturated or unsaturated, heterocyclic ring optionally contain-
ing one or more further heteroatoms selected from nitrogen, oxygen and sulfur,
and optionally substituted with C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy,
amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, aryl-
sulfonyl, arylamino or heteroarylamino;

25

R³, R⁴, R⁵ and R⁶ independently are

hydrogen, carboxy, C₁₋₆-alkoxycarbonyl, cyano, trifluoromethyl, halogen,

30 C₃₋₈-cycloalkyl optionally substituted with

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

5 C₁₋₆-alkyl, C₂₋₆-alkenyl or C₂₋₆-alkynyl, which are optionally substituted with C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, cyano, halogen, trifluoromethyl, carboxy, C₁₋₆-alkoxycarbonyl,

10 C₃₋₈-cycloalkyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino, which are optionally substituted with C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroarylamino or -CO-NR⁹R¹⁰,

15 aryl optionally substituted with halogen, cyano, nitro, C₁₋₆-alkyl, C₁₋₆-alkoxy, hydroxy, trifluoromethyl, aryl, heteroaryl, aryloxy, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroarylamino or -CO-NR⁹R¹⁰,

20 -CO-NR⁹R¹⁰,

wherein R⁹ and R¹⁰ independently are

hydrogen,

25

C₁₋₆-alkyl optionally substituted with

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroaryl-amino or C₃₋₈-cycloalkyl, which are optionally substituted with

30 C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, aryl-amino or heteroarylamino,

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl or heteroarylsulfonyl, which are optionally substituted with

5 C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

C₁₋₆-alkylsulfonyl optionally substituted with

10 C₃₋₈-cycloalkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino, or

15 R⁹ and R¹⁰, together with the nitrogen atom to which they are connected, form a 3 to 8 membered, saturated or unsaturated, heterocyclic ring optionally containing one or more further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally substituted with C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino, or

20 R³ and R⁴, together with the carbon atom to which they are connected, and/or R⁵ and R⁶ together with the carbon atom to which they are connected, form a 3 to 8 membered, saturated or unsaturated, carbocyclic or heterocyclic ring optionally substituted with C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, halogen, cyano, 25 trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

m, n, p and q independently are 0, 1 or 2;

30 X is a valence bond, -CH₂-, -C(=O)-, -C(=S)-, -S(=O)-, -S(=O)₂-, -C(=N-CN)-, -C(=CH-NO₂)-, -C[=C(CN)₂]-, -C(=CH-CN)- or -C(=NR¹¹)-,

wherein R¹¹ is

hydrogen,

5

C₁₋₆-alkyl optionally substituted with

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroaryl-
amino or C₃₋₈-cycloalkyl, which are optionally substituted with

10 C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, halogen, cyano,
trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, aryl-
amino or heteroaryl-amino,

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl or heteroarylsulfonyl, which are
optionally substituted with

15 C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, halogen, cyano,
trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino
or heteroaryl-amino,

C₁₋₆-alkylsulfonyl optionally substituted with

20 C₃₋₈-cycloalkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, halogen, cyano,
trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino
or heteroaryl-amino;

Y is a valence bond, -O- or -N(R¹²)-,

25

wherein R¹² is

hydrogen,

30

C₁₋₆-alkyl optionally substituted with

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroaryl-amino or C₃₋₈-cycloalkyl, which are optionally substituted with

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, aryl-amino or heteroarylamino,

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl or heteroarylsulfonyl, which are optionally substituted with

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

C₁₋₆-alkylsulfonyl optionally substituted with

C₃₋₈-cycloalkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

A is a valence bond, C₁₋₈-alkylene, C₂₋₈-alkenylene, C₂₋₈-alkynylene, C₃₋₈-cycloalkylene or phenylene, or

when Y is -N(R¹²)-, A, together with R¹² and the nitrogen atom to which they are connected, may form a 3 to 8 membered, saturated or unsaturated, heterocyclic ring system optionally containing one or more further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally substituted with C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aryl-C₁₋₆-alkyl, heteroaryl-C₁₋₆-alkyl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino; and

Z is -R¹³, -OR¹³, -SR¹³, -NR¹³R¹⁴, -CHR¹³R¹⁴, -CR¹³R¹⁴R¹⁵ or =CR¹³R¹⁴,

wherein R¹³, R¹⁴ and R¹⁵ independently are

hydrogen,

C₁₋₆-alkyl, C₂₋₆-alkenyl or C₂₋₆-alkynyl, which are optionally substituted with

aryl, arylamino, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, C₁₋₆-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, heteroaryl or C₃₋₈-cycloalkyl, which are optionally substituted with

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, aryl-C₁₋₆-alkyl, heteroaryl-C₁₋₆-alkyl, nitro, arylamino, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C₁₋₆-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, hydroxy, amino, halogen, cyano or trifluoromethyl,

aryl, C₃₋₁₅-cycloalkyl, aroyl or heteroaryl, which are optionally substituted with

aryl-C₁₋₆-alkyl, heteroaryl-C₁₋₆-alkyl, aryl, heteroaryl, nitro, arylamino, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C₁₋₆-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl, where

R¹³ and R¹⁴ or R¹³, R¹⁴ and R¹⁵, when they do not represent hydrogen, may be joined by one or more bridging linkers such as a valence bond, C₁₋₄-alkylene, C₂₋₄-alkenylene, -O-, -S-, -N(R¹⁶)-, -C(=O)-, -S(=O)-, -S(=O)₂-, -C(R¹⁶R¹⁷)-, phenylene, biphenylene, -O-C₁₋₄-alkylene, -S-C₁₋₄-alkylene, -N(R¹⁶)-C₁₋₄-alkylene, -N=C₁₋₄-alkylene, -O-C₂₋₄-alkenylene, -S-C₂₋₄-alkenylene or -N(R¹⁶)-C₂₋₄-alkenylene, to form a mono-, bi- or polycyclic ring system,

wherein R¹⁶ and R¹⁷ independently are

hydrogen,

C₁₋₆-alkyl optionally substituted with

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, hetero-
arylamino or C₃₋₈-cycloalkyl, which are optionally substituted with

5 C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, halogen,
cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, aryl-
sulfonyl, arylamino or heteroarylamino,

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl or heteroarylsulfonyl, which
are optionally substituted with

10 C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, halogen, cyano,
trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, aryl-
amino or heteroarylamino,

C₁₋₆-alkylsulfonyl optionally substituted with

15 C₃₋₈-cycloalkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, halogen,
cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsul-
fonyl, arylamino or heteroarylamino, or

20 R¹⁶ and R¹⁷, together with the nitrogen atom to which they are connected,
form a 3 to 8 membered, saturated or unsaturated, heterocyclic ring op-
tionally containing one or more further heteroatoms selected from nitro-
gen, oxygen and sulfur, and optionally substituted with C₁₋₆-alkyl,
C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl,
aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroaryl-
25 amino;

with the provisos that

when X is -CS-, R¹ = R² = R⁵ = R⁶ = hydrogen, m = n = p = 0 and q = 1, the group
30 -Y-A-Z must not start with the radical -NH-;

when the group -X-Y-A-Z starts with the radical -CH₂-, R¹ = R² = R⁶ = hydrogen, m = n = p = 0 and q = 1, R⁵ must not be carboxy or aminocarbonyl;

5 when X is -CO-, the group -Y-A-Z starts with the radical -NH-, R¹ = R² = R⁶ = hydrogen, m = n = p = 0 and q = 1, the remainder of the group -Y-A-Z must not be hydrogen, unsubstituted or C₁₋₆-alkoxy substituted phenyl, unsubstituted C₃₋₆-cycloalkyl or unsubstituted C₁₋₆-alkyl;

10 when X is -CO-, Y is -O-, A is -CH₂-, Z is phenyl, R¹ = R² = R³ = R⁴ = R⁶ = hydrogen, m = n = p = 0 and q = 1, R⁵ must not be carboxy, aminocarbonyl or 4-phenyl-piperazin-1-ylcarbonyl;

15 when X is -CO-, Y is -O-, A is -CH₂-, Z is phenyl, R¹ = R³ = R⁴ = R⁶ = hydrogen, R² = butyl, m = n = p = 0 and q = 1, R⁵ must not be methoxycarbonyl;

when X is -CO-, Y is -O-, A is -CH₂-, Z is phenyl, R¹ = R² = R⁴ = R⁵ = R⁶ = hydrogen, m = n = p = 0 and q = 1, R³ must not be hydrogen, ethyl, isopropyl or phenyl;

20 when X is -CO-, Y is -O-, A is a valence bond, Z is *tert*-butyl, R¹ = R² = R³ = R⁴ = R⁶ = hydrogen, m = n = p = 0 and q = 1, R⁵ must not be carboxy;

when X is -CO-, Y is -O-, A is a valence bond, Z is *tert*-butyl, R¹ = R² = R⁴ = R⁵ = R⁶ = hydrogen, m = n = p = 0 and q = 1, R³ must not be 4-cyanophenyl;

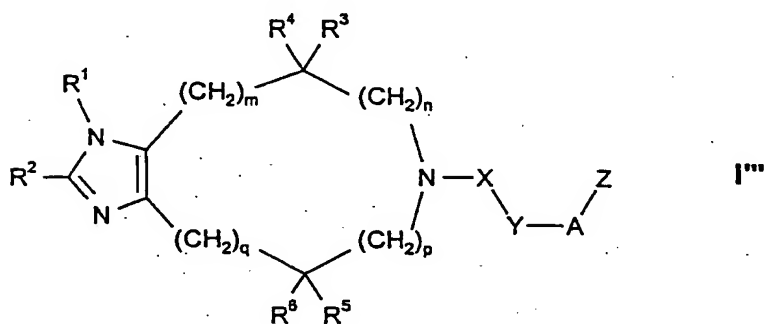
25 when X is -CO-, the group -Y-A-Z starts with the radical -O-, R¹ = R² = R⁶ = hydrogen, m = n = p = 0 and q = 1, R⁵ must not be carboxy, aminocarbonyl or hydrogen;

30 when -X is -CO-, the group -Y-A-Z starts with the radical -CH<, R¹ = R² = R³ = R⁴ = R⁶ = hydrogen, m = n = p = 0 and q = 1, R⁵ must not be hydroxymethyl, C₁₋₆-alkoxy-carbonyl or carboxy; and

when X is -CO-, the group -Y-A-Z is 4-methoxyphenyl, $R^1 = R^2 = R^3 = R^4 = R^5 = \text{hydrogen}$, $m = n = p = 0$ and $q = 1$, R^5 must not be carboxy;

as well as any optical or geometric isomer or tautomeric form thereof including mix-
 5 tures of these or a pharmaceutically acceptable salt thereof.

In a further aspect the invention relates to novel, substituted imidazoles of the ge-
 neral formula I'''



wherein

R^1 is hydrogen or a functional group which can be converted to hydrogen *in vivo*;

R^2 is hydrogen, C_{1-6} -alkyl, halogen, cyano, trifluoromethyl, hydroxy or $-NR^7R^8$

wherein R^7 and R^8 independently are

hydrogen;

C_{1-6} -alkyl optionally substituted with aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroaryl amino or C_{3-8} -cycloalkyl which are optionally substituted with C_{1-6} -alkyl, C_{1-6} -alkoxy, C_{1-6} -alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroaryl amino;

aryl optionally substituted with C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, aryl-amino or heteroarylamino;

5

heteroaryl optionally substituted with C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

- 10 aroyl optionally substituted with C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, aryl-amino or heteroarylamino;

- heteroaroyl optionally substituted with C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy,
15 amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

- arylsulfonyl optionally substituted with C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-C₁₋₆-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl,
20 arylsulfonyl, arylamino or heteroarylamino;

- heteroarylsulfonyl optionally substituted with C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino; or

25

C₁₋₆-alkylsulfonyl optionally substituted with C₃₋₈-cycloalkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino; or

- 30 R⁷ and R⁸, together with the nitrogen atom to which they are connected, form a 3 to 8 membered, saturated or unsaturated, carbocyclic or heterocyclic ring optionally sub-

stituted with C₁₋₈-alkyl, C₁₋₈-alkoxy, C₁₋₈-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

5 R³, R⁴, R⁵ and R⁶ independently are

hydrogen; carboxy; C₁₋₈-alkoxycarbonyl; -CO-NR⁷R⁸ wherein R⁷ and R⁸ are as defined above; cyano; or halogen;

10 C₃₋₈-cycloalkyl optionally substituted with C₁₋₈-alkyl, C₁₋₈-alkoxy, C₁₋₈-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

C₁₋₈-alkyl optionally substituted with

15 C₁₋₈-alkoxy; C₁₋₈-alkylthio; hydroxy; cyano; halogen; trifluoromethyl; carboxy; C₁₋₈-alkoxycarbonyl; or -CO-NR⁷R⁸ wherein R⁷ and R⁸ are as defined above; or C₃₋₈-cycloalkyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino which are optionally substituted with C₁₋₈-alkyl, C₁₋₈-alkoxy, C₁₋₈-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl,
20 aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

C₂₋₆-alkenyl optionally substituted with

C₁₋₈-alkoxy; C₁₋₈-alkylthio; hydroxy; cyano; halogen; trifluoromethyl; carboxy; C₁₋₈-alkoxycarbonyl; or -CO-NR⁷R⁸ wherein R⁷ and R⁸ are as defined above; or
25 C₃₋₈-cycloalkyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino which are optionally substituted with C₁₋₈-alkyl, C₁₋₈-alkoxy, C₁₋₈-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

30 C₂₋₆-alkynyl optionally substituted with

C₁₋₈-alkoxy; C₁₋₈-alkylthio; hydroxy; cyano; halogen; trifluoromethyl; carboxy; C₁₋₈-alkoxycarbonyl; or -CO-NR⁷R⁸ wherein R⁷ and R⁸ are as defined above; or C₃₋₈-cycloalkyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino which are optionally substituted with C₁₋₈-alkyl, C₁₋₈-alkoxy, C₁₋₈-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino; or

aryl optionally substituted with halogen, cyano, nitro, C₁₋₈-alkyl, C₁₋₈-alkoxy, hydroxy, trifluoromethyl, aryl, heteroaryl, aryloxy, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroarylamino or -CO-NR⁷R⁸ wherein R⁷ and R⁸ are as defined above; or

R³ and R⁴, together with the carbon atom to which they are connected, and/or R⁵ and R⁶ together with the carbon atom to which they are connected, form a 3 to 8 membered, saturated or unsaturated, carbocyclic or heterocyclic ring optionally substituted with C₁₋₈-alkyl, C₁₋₈-alkoxy, C₁₋₈-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

m, n, p and q independently are 0, 1 or 2;

X is a valence bond, -CH₂-, -C(=O)-, -C(=S)-, -S(=O)-, -S(=O)₂-, -C(=N-CN)-, -C(=CH-NO₂)-, -C[=C(CN)₂]-, -C(=CH-CN)-, or -C(=NR⁷)- wherein R⁷ is as defined above;

Y is a valence bond, -O- or -N(R⁷)- wherein R⁷ is as defined above;

A is a valence bond, C₁₋₈-alkylene, C₂₋₈-alkenylene, C₂₋₈-alkynylene, C₃₋₈-cycloalkylene or phenylene; or

when Y is -N(R⁷)-, A may together with R⁷ form a 3 to 8 membered, saturated or unsaturated, carbocyclic or heterocyclic ring optionally substituted with C₁₋₈-alkyl,

C₁₋₈-alkoxy, C₁₋₈-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino; and

Z is -R⁹, -OR⁹, -SR⁹, -NR⁹R¹⁰, -CHR⁹R¹⁰ or =CR⁹R¹⁰

5

wherein R⁹ and R¹⁰ independently are

hydrogen;

- 10 C₁₋₈-alkyl optionally substituted with aryl, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, C₁₋₈-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryl-oxy, acylamino, heteroaryl or C₃₋₈-cycloalkyl which are optionally substituted with C₁₋₈-alkyl, C₁₋₈-alkoxy, C₁₋₈-alkylthio, aryl-C₁₋₈-alkyl, heteroaryl-C₁₋₈-alkyl, nitro, aryl-amino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C₁₋₈-alkyl-
15 sulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, hydroxy, amino, halogen, cyano or trifluoromethyl;

- C₂₋₆-alkenyl optionally substituted with aryl, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, C₁₋₈-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryl-
20 oxy, acylamino, heteroaryl or C₃₋₈-cycloalkyl which are optionally substituted with C₁₋₈-alkyl, C₁₋₈-alkoxy, C₁₋₈-alkylthio, aryl-C₁₋₈-alkyl, heteroaryl-C₁₋₈-alkyl, nitro, aryl-amino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C₁₋₈-alkyl-sulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, hydroxy, amino, halogen, cyano or trifluoromethyl;

25

- C₂₋₆-alkynyl optionally substituted with aryl, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, C₁₋₈-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, heteroaryl or C₃₋₈-cycloalkyl which are optionally substituted with C₁₋₈-alkyl, C₁₋₈-alkoxy, C₁₋₈-alkylthio, aryl-C₁₋₈-alkyl, heteroaryl-C₁₋₈-alkyl, nitro, aryl-
30 amino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C₁₋₈-alkyl-

sulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, hydroxy, amino, halogen, cyano or trifluoromethyl;

aryl optionally substituted with aryl-C₁₋₆-alkyl, heteroaryl-C₁₋₆-alkyl, aryl, heteroaryl,
 5 nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl,
 C₁₋₆-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino,
 C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, halogen, cyano or trifluoro-
 methyl;

10 C₃₋₁₅-cycloalkyl optionally substituted with aryl-C₁₋₆-alkyl, heteroaryl-C₁₋₆-alkyl, aryl,
 heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, hetero-
 arylsulfonyl, C₁₋₆-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acyl-
 amino, C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, halogen, cyano or
 trifluoromethyl;

15 aroyl optionally substituted with aryl-C₁₋₆-alkyl, heteroaryl-C₁₋₆-alkyl, aryl, heteroaryl,
 nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl,
 C₁₋₆-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino,
 C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, halogen, cyano or trifluoro-
 20 methyl; or

heteroaryl optionally substituted with aryl-C₁₋₆-alkyl, heteroaryl-C₁₋₆-alkyl, aryl, het-
 eroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroaryl-
 sulfonyl, C₁₋₆-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino,
 25 C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, halogen, cyano or trifluoro-
 methyl; or

R⁹ and R¹⁰ are joined by one or more bridging linkers such as a valence bond,
 C₁₋₄-alkylene, C₂₋₄-alkenylene, -O-, -S-, -N(R⁷)-, -C(=O)-, -S(=O)-, -S(=O)₂-, -C(R⁷R⁸)-,
 30 phenylene, biphenylene, -O-C₁₋₄-alkylene, -S-C₁₋₄-alkylene, -N(R⁷)-C₁₋₄-alkylene,

-N=C₁₋₄-alkylene, -O-C₂₋₄-alkenylene, -S-C₂₋₄-alkenylene, or -N(R⁷)-C₂₋₄-alkenylene, to form a mono-, bi- or polycyclic ring system; or

when Y is -N(R⁷)-, R⁹ or R¹⁰ may together with R⁷ form a 3 to 8 membered, saturated or unsaturated, carbocyclic or heterocyclic ring optionally substituted with
 5 aryl-C₁₋₆-alkyl, heteroaryl-C₁₋₆-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C₁₋₆-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl;

10

with the provisos that

when X is -CS-, R¹ = R² = R⁵ = R⁶ = hydrogen, m = n = p = 0 and q = 1, the group -Y-A-Z must not start with the radical -NH-;

15

when the group -X-Y-A-Z starts with the radical -CH₂-, R¹ = R² = R⁶ = hydrogen, m = n = p = 0 and q = 1, R⁵ must not be carboxy or aminocarbonyl;

when X is -CO-, the group -Y-A-Z starts with the radical -NH-, R¹ = R² = R⁶ = hydrogen, m = n = p = 0 and q = 1, the remainder of the group -Y-A-Z must not be hydrogen, unsubstituted or C₁₋₆-alkoxy substituted phenyl, unsubstituted C₃₋₈-cycloalkyl or unsubstituted C₁₋₆-alkyl;

20

when X is -CO-, the group -Y-A-Z starts with the radical -O-, R¹ = R² = R⁶ = hydrogen, m = n = p = 0 and q = 1, R⁵ must not be carboxy, aminocarbonyl or hydrogen;

25

when -X is -CO-, the group -Y-A-Z starts with the radical -CH<, R¹ = R² = R³ = R⁴ = R⁶ = hydrogen, m = n = p = 0 and q = 1, R⁵ must not be hydroxymethyl, C₁₋₆-alkoxycarbonyl or carboxy; and

30

when X is -CO-, the group -Y-A-Z is 4-methoxyphenyl, $R^1 = R^2 = R^3 = R^4 = R^6 =$ hydrogen, $m = n = p = 0$ and $q = 1$, R^5 must not be carboxy;

and a pharmaceutically acceptable salt thereof or any optical isomer thereof or mixture of optical isomers, including a racemic mixture, or any tautomeric form.

Preferred embodiments thereof are as disclosed above for formula I.

The compounds of the present invention may have one or more asymmetric centres and it is intended that any optical isomers, as separated, pure or partially purified optical isomers or racemic mixtures thereof are included in the scope of the invention.

Furthermore, when a double bond or a fully or partially saturated ring system is present in the molecule geometric isomers may be formed. It is intended that any geometric isomers, as separated, pure or partially purified geometric isomers or mixtures thereof are included within the scope of the invention. Likewise, molecules having a bond with restricted rotation may form geometric isomers. These are also intended to be included within the scope of the present invention.

Furthermore, the compounds of the present invention may exist in different tautomeric forms and it is intended that any tautomeric forms, which the compounds are able to form, are included within the scope of the present invention.

The present invention also encompasses pharmaceutically acceptable salts of the present compounds. Such salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts, ammonium and alkylated ammonium salts. Acid addition salts include salts of inorganic acids as well as organic acids. Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric acids and the like. Representative examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, lactic, maleic, malic, malonic,

mandelic, oxalic, picric, pyruvic, salicylic, succinic, methanesulfonic, ethanesulfonic, tartaric acids and the like. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in *J. Pharm. Sci.* **1977**, *66*, *2*, which is incorporated herein by reference.

- 5 Examples of metal salts include lithium, sodium, potassium, magnesium salts and the like. Examples of ammonium and alkylated ammonium salts include ammonium, methylammonium, dimethylammonium, trimethylammonium, ethylammonium, hydroxyethylammonium, diethylammonium, butylammonium, tetramethylammonium salts and the like.

10

Also intended as pharmaceutically acceptable acid addition salts are the hydrates, which the present compounds, are able to form.

- 15 The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent.

- 20 The compounds of the present invention may form solvates with standard low molecular weight solvents using methods known to the skilled artisan. Such solvates are also contemplated as being within the scope of the present invention.

- 25 The invention also encompasses prodrugs of the present compounds, which on administration undergo chemical conversion by metabolic processes before becoming active pharmacological substances. In general, such prodrugs will be functional derivatives of the compounds, which are readily convertible *in vivo* into the present compounds. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

30

The invention also encompasses active metabolites of the present compounds.

The compounds of the present invention interact with the histamine H3 receptor and may thus be used for the treatment of a wide range of conditions and disorders in which histamine H3 receptor interactions are beneficial.

5

Accordingly, in another aspect the present invention relates to a compound of the general formula I as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof for use as a medicament.

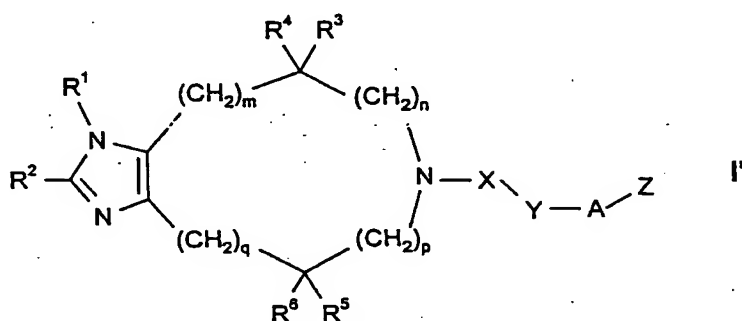
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The invention also relates to pharmaceutical compositions comprising, as an active ingredient, at least one compound of the formula I as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof together with one or more pharmaceutically acceptable

15

carriers or diluents.

Furthermore, the invention relates to the use of a compound of the general formula I'



20

wherein

R¹ is hydrogen or a functional group, which can be converted to hydrogen *in vivo*;

R² is hydrogen, C₁₋₆-alkyl, halogen, cyano, trifluoromethyl, trifluoromethoxy, hydroxy or -NR⁷R⁸,

wherein R⁷ and R⁸ independently are

5

hydrogen,

C₁₋₆-alkyl optionally substituted with

10

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroaryl-amino or C₃₋₈-cycloalkyl, which are optionally substituted with

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

15

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl or heteroarylsulfonyl, which are optionally substituted with

20

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

C₁₋₆-alkylsulfonyl optionally substituted with

25

C₃₋₈-cycloalkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino, or

30

R⁷ and R⁸, together with the nitrogen atom to which they are connected, form a 3 to 8 membered, saturated or unsaturated, heterocyclic ring optionally containing one or more further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally substituted with C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy,

amino, C₁₋₈-alkylamino, di(C₁₋₈-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

5 R³, R⁴, R⁵ and R⁶ independently are

hydrogen, carboxy, C₁₋₈-alkoxycarbonyl, cyano, trifluoromethyl, halogen,

C₃₋₈-cycloalkyl optionally substituted with

10 C₁₋₈-alkyl, C₁₋₈-alkoxy, C₁₋₈-alkylthio, hydroxy, amino, C₁₋₈-alkylamino, di(C₁₋₈-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

C₁₋₈-alkyl, C₂₋₈-alkenyl or C₂₋₈-alkynyl, which are optionally substituted with

15 C₁₋₈-alkoxy, C₁₋₈-alkylthio, hydroxy, cyano, halogen, trifluoromethyl, trifluoromethoxy, carboxy, C₁₋₈-alkoxycarbonyl,

C₃₋₈-cycloalkyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino, which are optionally substituted with

20 C₁₋₈-alkyl, C₁₋₈-alkoxy, C₁₋₈-alkylthio, hydroxy, amino, C₁₋₈-alkylamino, di(C₁₋₈-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroarylamino or -CO-NR⁹R¹⁰,

25 aryl optionally substituted with

halogen, cyano, nitro, C₁₋₈-alkyl, C₁₋₈-alkoxy, hydroxy, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aryloxy, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroarylamino or -CO-NR⁹R¹⁰,

30 -CO-NR⁹R¹⁰,

wherein R⁹ and R¹⁰ independently are

hydrogen,

5 C₁₋₈-alkyl optionally substituted with

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroaryl-amino or C₃₋₈-cycloalkyl, which are optionally substituted with

C₁₋₈-alkyl, C₁₋₈-alkoxy, C₁₋₈-alkylthio, hydroxy, amino, C₁₋₈-alkylamino,
di(C₁₋₈-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy,
10 aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl or heteroarylsulfonyl, which are optionally substituted with

15 C₁₋₈-alkyl, C₁₋₈-alkoxy, C₁₋₈-alkylthio, hydroxy, amino, C₁₋₈-alkylamino, di(C₁₋₈-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

C₁₋₈-alkylsulfonyl optionally substituted with

20 C₃₋₈-cycloalkyl, C₁₋₈-alkoxy, C₁₋₈-alkylthio, hydroxy, amino, C₁₋₈-alkylamino, di(C₁₋₈-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino, or

25 R⁹ and R¹⁰, together with the nitrogen atom to which they are connected, form a 3 to 8 membered, saturated or unsaturated, heterocyclic ring optionally containing one or more further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally substituted with C₁₋₈-alkyl, C₁₋₈-alkoxy, C₁₋₈-alkylthio, hydroxy, amino, C₁₋₈-alkylamino, di(C₁₋₈-alkyl)amino, halogen, cyano, trifluoromethyl,
30 trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino, or

R³ and R⁴, together with the carbon atom to which they are connected, and/or R⁵ and R⁶ together with the carbon atom to which they are connected, form a 3 to 8 membered, saturated or unsaturated, carbocyclic or heterocyclic ring optionally substituted with C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

m, n, p and q independently are 0, 1 or 2;

X is a valence bond, -CH₂-, -C(=O)-, -C(=S)-, -S(=O)-, -S(=O)₂-, -C(=N-CN)-, -C(=CH-NO₂)-, -C[=C(CN)₂]-, -C(=CH-CN)-, -C(=NR¹¹)- or -C(=N-S(=O)₂R^{11a})-,

wherein R¹¹ is

hydrogen,

C₁₋₆-alkyl optionally substituted with

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroaryl-amino or C₃₋₈-cycloalkyl, which are optionally substituted with

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl or heteroarylsulfonyl, which are optionally substituted with

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

C₁₋₈-alkylsulfonyl optionally substituted with

C₃₋₈-cycloalkyl, C₁₋₈-alkoxy, C₁₋₈-alkylthio, hydroxy, amino, C₁₋₈-alkylamino, di(C₁₋₈-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

5

R^{11a} is

C₁₋₈-alkyl optionally substituted with

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroaryl-amino or C₃₋₈-cycloalkyl, which are optionally substituted with

10

C₁₋₈-alkyl, C₁₋₈-alkoxy, C₁₋₈-alkylthio, hydroxy, amino, C₁₋₈-alkylamino, di(C₁₋₈-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

15

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl or heteroarylsulfonyl, which are optionally substituted with

C₁₋₈-alkyl, C₁₋₈-alkoxy, C₁₋₈-alkylthio, hydroxy, amino, C₁₋₈-alkylamino, di(C₁₋₈-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

20

Y is a valence bond, -O- or -N(R¹²)-,

wherein R¹² is

25

hydrogen,

C₁₋₈-alkyl optionally substituted with

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroaryl-amino or C₃₋₈-cycloalkyl, which are optionally substituted with

30

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

5

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl or heteroarylsulfonyl, which are optionally substituted with

10

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

C₁₋₆-alkylsulfonyl optionally substituted with

15

C₃₋₈-cycloalkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

A is a valence bond, C₁₋₈-alkylene, C₂₋₈-alkenylene, C₂₋₈-alkynylene, C₃₋₈-cycloalkylene or phenylene, or

20

when Y is -N(R¹²)-, A, together with R¹² and the nitrogen atom to which they are connected, may form a 3 to 8 membered, saturated or unsaturated, heterocyclic ring system optionally containing one or more further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally substituted with C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aryl-C₁₋₆-alkyl, heteroaryl-C₁₋₆-alkyl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino; and

25

30

Z is -R¹³, -OR¹³, -SR¹³, -NR¹³R¹⁴, -CHR¹³R¹⁴, -CR¹³R¹⁴R¹⁵ or =CR¹³R¹⁴,

wherein R¹³, R¹⁴ and R¹⁵ independently are

hydrogen,

C₁₋₈-alkyl, C₂₋₈-alkenyl or C₂₋₈-alkynyl, which are optionally substituted with

aryl, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, C₁₋₈-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, heteroaryl or C₃₋₈-cycloalkyl, which are optionally substituted with

C₁₋₈-alkyl, C₁₋₈-alkoxy, C₁₋₈-alkylthio, aryl-C₁₋₈-alkyl, heteroaryl-C₁₋₈-alkyl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C₁₋₈-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, hydroxy, amino, C₁₋₈-alkylamino, di(C₁₋₈-alkyl)amino, halogen, cyano, trifluoromethoxy or trifluoromethyl,

aryl, C₃₋₁₅-cycloalkyl, C₃₋₁₅-cycloalkenyl, C₃₋₁₅-cycloalkynyl, aroyl or heteroaryl, which are optionally substituted with

aryl-C₁₋₈-alkyl, heteroaryl-C₁₋₈-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C₁₋₈-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C₁₋₈-alkyl, C₁₋₈-alkoxy, C₁₋₈-alkylthio, C₃₋₈-cycloalkanecarbonyl, hydroxy, amino, C₁₋₈-alkylamino, di(C₁₋₈-alkyl)amino, halogen, cyano, trifluoromethoxy or trifluoromethyl, where

R¹³ and R¹⁴ or R¹³, R¹⁴ and R¹⁵, when they do not represent hydrogen, may be joined by one or more bridging linkers such as a valence bond, C₁₋₄-alkylene, C₂₋₄-alkenylene, -O-, -S-, -N(R¹⁶)-, -C(=O)-, -S(=O)-, -S(=O)₂-, -C(R¹⁶R¹⁷)-, phenylene, biphenylene, -O-C₁₋₄-alkylene, -S-C₁₋₄-alkylene, -N(R¹⁶)-C₁₋₄-alkylene, -N=C₁₋₄-alkylene, -O-C₂₋₄-alkenylene, -S-C₂₋₄-alkenylene or -N(R¹⁶)-C₂₋₄-alkenylene, to form a mono-, bi- or polycyclic ring system,

wherein R¹⁶ and R¹⁷ independently are

hydrogen,

C₁₋₈-alkyl optionally substituted with

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroarylamino or C₃₋₈-cycloalkyl, which are optionally substituted with C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl or heteroarylsulfonyl, which are optionally substituted with

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

C₁₋₆-alkylsulfonyl optionally substituted with

C₃₋₈-cycloalkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino, or

R¹⁶ and R¹⁷, together with the nitrogen atom to which they are connected, form a 3 to 8 membered, saturated or unsaturated, heterocyclic ring optionally containing one or more further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally substituted with C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

as well as any optical or geometric isomer or tautomeric form thereof including mix-
tures of these or a pharmaceutically acceptable salt thereof for the preparation of a
medicament for the treatment and/or prevention of disorders and diseases related to
5 the histamine H₃ receptor.

In still another aspect, the invention relates to a method for the treatment of disorders
related to the histamine H₃ receptor the method comprising administering to a
subject in need thereof an effective amount of a compound of the formula I' as well
10 as any optical or geometric isomer or tautomeric form thereof including mixtures of
these or a pharmaceutically acceptable salt thereof or a pharmaceutical composition
comprising the same.

More particularly, the present compounds may possess histamine H₃ receptor
15 antagonistic activity and would accordingly be useful in the treatment of a wide range
of conditions and disorders in which a histamine H₃ receptor blockade is beneficial.

In a preferred embodiment of the invention the present compounds are used for the
preparation of a pharmaceutical composition for the reduction of weight.

20 In a preferred embodiment of the invention the present compounds are used for the
preparation of a pharmaceutical composition for the treatment and/or prevention of
overweight or obesity.

25 In another preferred embodiment of the invention the present compounds are used
for the preparation of a pharmaceutical composition for the suppression of appetite
or satiety induction.

In a further preferred embodiment of the invention the present compounds are used
30 for the preparation of a pharmaceutical composition for the prevention and/or treat-
ment of disorders and diseases related to overweight or obesity such as atheroscle-

rosis, hypertension, IGT (impaired glucose tolerance), diabetes, especially Type 2 diabetes (NIDDM (non-insulin dependent diabetes mellitus)), dyslipidaemia, coronary heart disease, gallbladder disease, osteoarthritis and various types of cancer such as endometrial, breast, prostate and colon cancers.

5

In yet a further preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the prevention and/or treatment of eating disorders such as bulimia and binge eating.

- 10 In a further preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of IGT.

- 15 In a further preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of Type 2 diabetes.

- 20 In another preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the delaying or prevention of the progression from IGT to Type 2 diabetes.

- 25 In a further preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the delaying or prevention of the progression from non-insulin requiring Type 2 diabetes to insulin requiring Type 2 diabetes.

The compounds of the present invention may also be used for the treatment of airway disorders such as asthma, as anti-diarrhoeals and for the modulation of gastric acid secretion.

30

Furthermore, the compounds of the present invention may be used for the treatment of diseases associated with the regulation of sleep and wakefulness and for the treatment of narcolepsy and attention deficit disorders.

- 5 Moreover, the compounds of the invention may be used as stimulants or as sedatives.

The present compounds may also be used for the treatment of conditions associated with epilepsy. Additionally, the present compounds may be used for the treatment of
10 motion sickness and vertigo. Furthermore, they may be useful as regulators of hypothalamo-hypophyseal secretion, antidepressants, modulators of cerebral circulation, and in the treatment of irritable bowel syndrome.

Further, the compounds of the present invention may be used for the treatment of
15 dementia and Alzheimer's disease.

The present novel compounds may also interact with the vanilloid receptors, the serotonin receptors, and the adrenergic receptors and may be useful for the treatment of diseases associated with these receptors. Hence, the compounds of the present
20 invention may be vanilloid receptor agonists, and thus be useful for the treatment of obesity by enhancement of the metabolic rate and energy expenditure. Further, by virtue of their interaction with the vanilloid receptor the compounds of the present invention may be useful for the treatment of pain or neurogenic inflammation or inflammatory painful conditions.

25

In a further preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of diseases and disorders related to the vanilloid receptor, such as for the treatment and/or prevention of pain, neurogenic inflammation or obesity.

30

Furthermore, the present compounds may interact with the 5-HT₃ receptor (serotonin-3-receptor) and may accordingly be useful as antiemetics, in particular the chemotherapy-induced emesis. Further potential applications of 5-HT₃ antagonists include treatment of central nervous system disorders such as anxiety, schizophrenia, drug abuse and withdrawal symptoms, and pathological and age-associated amnesia.

In a further preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of diseases and disorders related to the serotonin-3 receptor (5-HT₃), such as for the treatment of emesis.

Furthermore, the present compounds may interact with the adrenergic alpha-2 receptor and thus be useful for the treatment of hypertension and of conditions associated with overexpression or hypersensitization of the adrenergic alpha-2 receptor, especially obesity, withdrawal symptoms to an adrenergic alpha-2 agonist, neurological disorders (especially orthostatic hypotension), multiple system atrophy, diabetes mellitus, benign prostatic hyperplasia or drug induced sensitization of the adrenergic alpha-2 receptor. Moreover, the compounds of the present invention, by virtue of their interaction with the alpha-2 receptor, may be useful as sedatives and hypnotics (sleep inducing agents) or as stimulants.

In a further preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of diseases and disorders related to the alpha-2 adrenergic receptor, such as for use as a sleep inducing agent.

The present compounds may be administered in combination with one or more further pharmacologically active substances eg selected from antiobesity agents, antidiabetics, antihypertensive agents, agents for the treatment and/or prevention of complica-

tions resulting from or associated with diabetes and agents for the treatment and/or prevention of complications and disorders resulting from or associated with obesity.

Thus, in a further aspect of the invention the present compounds may be administered in combination with one or more antiobesity agents or appetite regulating agents.

Such agents may be selected from the group consisting of CART (cocaine amphetamine regulated transcript) agonists, NPY (neuropeptide Y) antagonists, MC4 (melanocortin 4) agonists, orexin antagonists, TNF (tumor necrosis factor) agonists, CRF (corticotropin releasing factor) agonists, CRF BP (corticotropin releasing factor binding protein) antagonists, urocortin agonists, β 3 agonists, MSH (melanocyte-stimulating hormone) agonists, MCH (melanocyte-concentrating hormone) antagonists, CCK (cholecystokinin) agonists, serotonin re-uptake inhibitors, serotonin and noradrenaline re-uptake inhibitors, mixed serotonin and noradrenergic compounds, 5HT (serotonin) agonists, bombesin agonists, galanin antagonists, growth hormone, growth hormone releasing compounds, TRH (thyrotropin releasing hormone) agonists, UCP 2 or 3 (uncoupling protein 2 or 3) modulators, leptin agonists, DA agonists (bromocriptin, doperxin), lipase/amylase inhibitors, PPAR (peroxisome proliferator-activated receptor) modulators, RXR (retinoid X receptor) modulators or TR β agonists.

In one embodiment of the invention the antiobesity agent is leptin.

In another embodiment the antiobesity agent is dexamphetamine or amphetamine.

In another embodiment the antiobesity agent is fenfluramine or dexfenfluramine.

In still another embodiment the antiobesity agent is sibutramine.

In a further embodiment the antiobesity agent is orlistat.

In another embodiment the antiobesity agent is mazindol or phentermine.

Suitable antidiabetics comprise insulin, GLP-1 (glucagon like peptide-1) derivatives
5 such as those disclosed in WO 98/08871 to Novo Nordisk A/S, which is incorporated
herein by reference as well as orally active hypoglycaemic agents.

The orally active hypoglycaemic agents preferably comprise sulphonylureas, bigua-
nides, meglitinides, oxadiazolidinediones, thiazolidinediones, glucosidase inhibitors,
10 glucagon antagonists such as those disclosed in WO 99/01423 to Novo Nordisk A/S
and Agouron Pharmaceuticals, Inc., GLP-1 agonists, potassium channel openers
such as those disclosed in WO 97/26265 and WO 99/03861 to Novo Nordisk A/S
which are incorporated herein by reference, insulin sensitizers, DPP-IV (dipeptidyl
peptidase-IV) inhibitors, inhibitors of hepatic enzymes involved in stimulation of glu-
15 coneogenesis and/or glycogenolysis, glucose uptake modulators, compounds modi-
fying the lipid metabolism such as antihyperlipidemic agents and antilipidemic
agents, compounds lowering food intake, PPAR and RXR agonists and agents act-
ing on the ATP-dependent potassium channel of the β -cells.

20 In one embodiment of the invention the present compounds are administered in
combination with insulin.

In a further embodiment the present compounds are administered in combination
with a sulphonylurea eg tolbutamide, glibenclamide, glipizide or glicazide.

25

In another embodiment the present compounds are administered in combination with
a biguanide eg metformin.

In yet another embodiment the present compounds are administered in combination
30 with a meglitinide eg repaglinide.

In still another embodiment the present compounds are administered in combination with a thiazolidinedione eg troglitazone, ciglitazone, pioglitazone, rosiglitazone or the compounds disclosed in WO 97/41097 to Dr. Reddy's Research Foundation.

- 5 Furthermore, the present compounds may be administered in combination with the insulin sensitizers disclosed in WO 99/19313 to Dr. Reddy's Research Foundation.

In a further embodiment the present compounds are administered in combination with an α -glucosidase inhibitor eg miglitol or acarbose.

10

In another embodiment the present compounds are administered in combination with an agent acting on the ATP-dependent potassium channel of the β -cells eg tolbutamide, glibenclamide, glipizide, glicazide or repaglinide.

- 15 Furthermore, the present compounds may be administered in combination with nateglinide.

In still another embodiment the present compounds are administered in combination with an antihyperlipidemic agent or antilipidemic agent eg cholestyramine, colestipol, 20 clofibrate, gemfibrozil, lovastatin, pravastatin, simvastatin, probucol or dextrothyroxine.

In a further embodiment the present compounds are administered in combination with more than one of the above-mentioned compounds eg in combination with a 25 sulphonylurea and metformin, a sulphonylurea and acarbose, repaglinide and metformin, insulin and a sulphonylurea, insulin and metformin, insulin and troglitazone, insulin and lovastatin, etc.

Furthermore, the present compounds may be administered in combination with one 30 or more antihypertensive agents. Examples of antihypertensive agents are β -blockers such as alprenolol, atenolol, timolol, pindolol, propranolol and metoprolol,

ACE (angiotensin converting enzyme) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, quinapril and ramipril, calcium channel blockers such as nifedipine, felodipine, nicardipine, isradipine, nimodipine, diltiazem and verapamil, and α -blockers such as doxazosin, urapidil, prazosin and terazosin. Further reference can be made to Remington: The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

It should be understood that any suitable combination of the compounds according to the invention with one or more of the above-mentioned compounds and optionally one or more further pharmacologically active substances are considered to be within the scope of the present invention.

PHARMACEUTICAL COMPOSITIONS

The compounds of the invention may be administered alone or in combination with pharmaceutically acceptable carriers or excipients, in either single or multiple doses. The pharmaceutical compositions according to the invention may be formulated with pharmaceutically acceptable carriers or diluents as well as any other known adjuvants and excipients in accordance with conventional techniques such as those disclosed in Remington: The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

The pharmaceutical compositions may be specifically formulated for administration by any suitable route such as the oral, rectal, nasal, pulmonary, topical (including buccal and sublingual), transdermal, intracisternal, intraperitoneal, vaginal and parenteral (including subcutaneous, intramuscular, intrathecal, intravenous and intradermal) route, the oral route being preferred. It will be appreciated that the preferred route will depend on the general condition and age of the subject to be treated, the nature of the condition to be treated and the active ingredient chosen.

Pharmaceutical compositions for oral administration include solid dosage forms such as capsules, tablets, dragees, pills, lozenges, powders and granules. Where appro-

priate, they can be prepared with coatings such as enteric coatings or they can be formulated so as to provide controlled release of the active ingredient such as sustained or prolonged release according to methods well-known in the art.

- 5 Liquid dosage forms for oral administration include solutions, emulsions, suspensions, syrups and elixirs.

Pharmaceutical compositions for parenteral administration include sterile aqueous and non-aqueous injectable solutions, dispersions, suspensions or emulsions as well
10 as sterile powders to be reconstituted in sterile injectable solutions or dispersions prior to use. Depot injectable formulations are also contemplated as being within the scope of the present invention.

Other suitable administration forms include suppositories, sprays, ointments, cremes,
15 gels, inhalants, dermal patches, implants etc.

A typical oral dosage is in the range of from about 0.001 to about 100 mg/kg body weight per day, preferably from about 0.01 to about 50 mg/kg body weight per day, and more preferred from about 0.05 to about 10 mg/kg body weight per day adminis-
20 tered in one or more dosages such as 1 to 3 dosages. The exact dosage will depend upon the frequency and mode of administration, the sex, age, weight and general condition of the subject treated, the nature and severity of the condition treated and any concomitant diseases to be treated and other factors evident to those skilled in the art.

25

The formulations may conveniently be presented in unit dosage form by methods known to those skilled in the art. A typical unit dosage form for oral administration one or more times per day such as 1 to 3 times per day may contain of from 0.05 to about 1000 mg, preferably from about 0.1 to about 500 mg, and more preferred from
30 about 0.5 mg to about 200 mg.

For parenteral routes, such as intravenous, intrathecal, intramuscular and similar administration, typically doses are in the order of about half the dose employed for oral administration.

- 5 The compounds of this invention are generally utilized as the free substance or as a pharmaceutically acceptable salt thereof. One example is an acid addition salt of a compound having the utility of a free base. When a compound according to the invention contains a free base such salts are prepared in a conventional manner by treating a solution or suspension of a free base of the compound according to the invention
- 10 with a chemical equivalent of a pharmaceutically acceptable acid, for example, inorganic and organic acids. Representative examples are mentioned above. Physiologically acceptable salts of a compound with a hydroxy group include the anion of said compound in combination with a suitable cation such as sodium or ammonium ion.
- 15 For parenteral administration, solutions of the present compounds in sterile aqueous solution, aqueous propylene glycol or sesame or peanut oil may be employed. Such aqueous solutions should be suitable buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. The aqueous solutions are particularly suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration.
- 20 The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

- Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solution and various organic solvents. Examples of solid carriers are lactose, terra
- 25 alba, sucrose, cyclodextrin, talc, gelatine, agar, pectin, acacia, magnesium stearate, stearic acid or lower alkyl ethers of cellulose. Examples of liquid carriers are syrup, peanut oil, olive oil, phospholipids, fatty acids, fatty acid amines, polyoxyethylene or water. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or
- 30 mixed with a wax. The pharmaceutical compositions formed by combining the compounds according to the invention and the pharmaceutically acceptable carriers are

then readily administered in a variety of dosage forms suitable for the disclosed routes of administration. The formulations may conveniently be presented in unit dosage form by methods known in the art of pharmacy.

- 5 Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules or tablets, each containing a predetermined amount of the active ingredient, and which may include a suitable excipient. These formulations may be in the form of powder or granules, as a solution or suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion.

10

- If a solid carrier is used for oral administration, the preparation may be tableted, placed in a hard gelatine capsule in powder or pellet form or it can be in the form of a troche or lozenge. The amount of solid carrier will vary widely but will usually be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation may be in the
- 15 form of a syrup, emulsion, soft gelatine capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

A typical tablet, which may be prepared by conventional tableting techniques, may contain:

20

Core:

Active compound (as free compound or salt thereof)	5.0 mg
Lactosum Ph. Eur.	67.8 mg
Cellulose, microcryst. (Avicel)	31.4 mg
25 Amberlite	1.0 mg
Magnesium stearate Ph. Eur.	q.s.

Coating:

HPMC approx.

9 mg

Mywacett 9-40 T* approx.

0.9 mg

5

*Acylated monoglyceride used as plasticizer for film coating.

If desired, the pharmaceutical composition of the invention may comprise the compound of the formula I' in combination with further pharmacologically active sub-

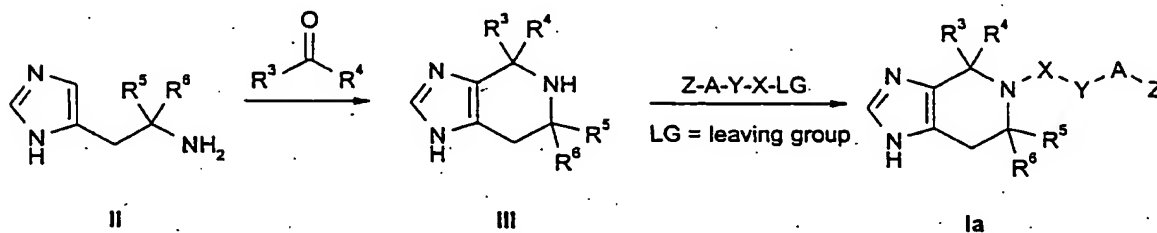
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stances.

The preparation of the compounds of this invention can be realized in many different ways. The preparation of imidazoles of the formula III has been described in the literature (see e.g. F. B. Stöcker et al., *J. Org. Chem.* **1966**, *31*, 2380; idem, *ibid.* **1990**, *55*, 3370; T. Vitali et al., *Il Farmaco* **1967**, *22*, 821; idem, *ibid.* **1965**, *20*, 634; S. Fränkel, K. Zeimer, *Biochemische Zeitschrift* **1920**, *110*, 238; G. Arcari et al., *Fr. Pat.* **1976**, *2 337 726*; DE 2700012, 1977, *Chem. Abstr.*, *87*, 201535).

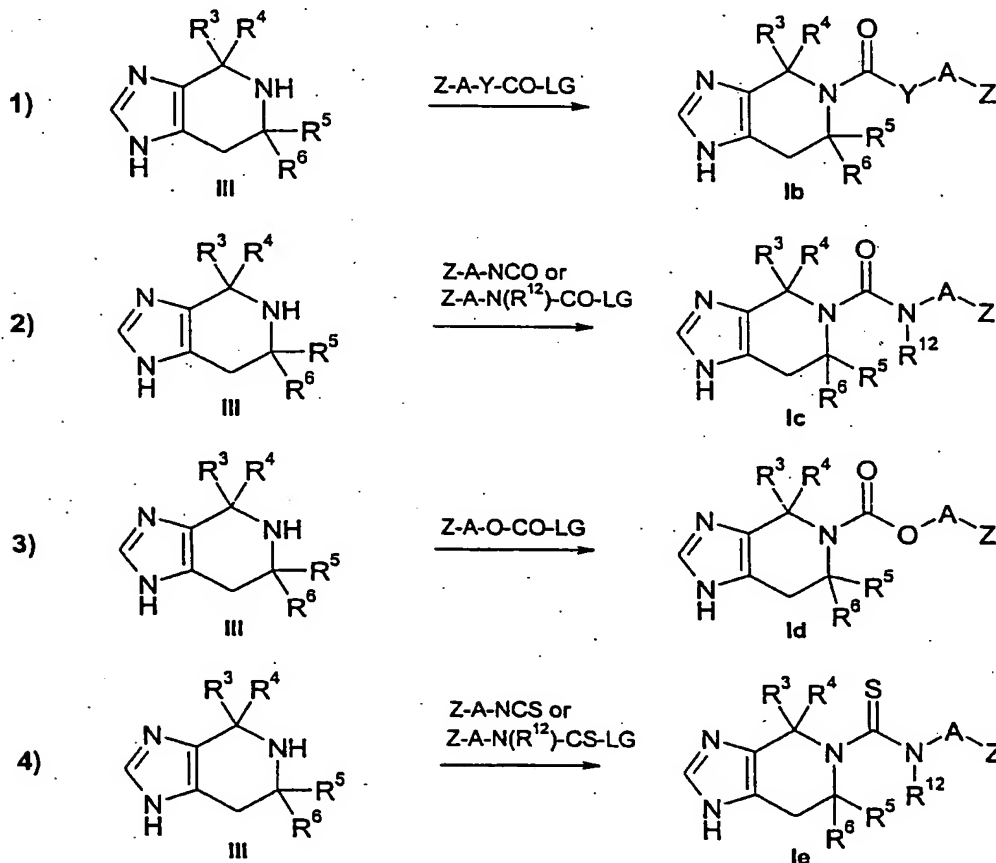
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Compounds of the formula Ia, wherein R^1 and R^2 are hydrogen, $m = n = p = 0$ and $q = 1$ can be prepared as outlined below:



5

More specifically, different types of compounds of the formula Ia of this invention can be prepared by the methods 1) to 4) sketched below:



LG = leaving group

For instance, compounds of the formula Ib can be synthesized from 4,5,6,7-tetrahydroimidazo[4,5-c]pyridines III by treating the latter with suitable activated derivatives of carboxylic acids, such as acyl imidazoles, anhydrides, acid chlorides or active esters, or any of the derivatives commonly used for the preparation of carboxamides, under appropriate conditions.

Compounds of the formula Ic can be prepared by treating 4,5,6,7-tetrahydroimidazo[4,5-c]pyridines III with isocyanates Z-A-NCO or with synthetic equivalents thereof, such as carbamoyl chlorides Z-A-N(R¹²)-CO-Cl under suitable conditions.

Compounds of the formula Id can be synthesized by treating 4,5,6,7-tetrahydroimidazo[4,5-c]pyridines III with haloformates Z-A-O-CO-Cl or with synthetic equivalents thereof such as activated carbonates (e.g. 4-nitrophenyl carbonates) under suitable conditions.

Finally, compounds of the formula Ie can be prepared by treating 4,5,6,7-tetrahydroimidazo[4,5-c]pyridines III with isothiocyanates Z-A-NCS or with synthetic equivalents thereof, such as thiocarbamoyl chlorides Z-A-N(R¹²)-CS-Cl under suitable conditions.

The starting materials are either known compounds or compounds, which may be prepared in analogy with the preparation of similar known compounds.

The present invention is further illustrated by the following representative examples, which are, however, not intended to limit the scope of the invention in any way.

EXAMPLES

In the examples the following terms are intended to have the following, general meanings:

DCM: dichloromethane, methylenechloride

DMF: *N,N*-dimethyl formamide

DMSO: dimethyl sulfoxide

EDC: *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide hydrochloride

HOBt: *N*-hydroxybenzotriazole, 1-hydroxybenzotriazole

NMP: *N*-methylpyrrolidone

5

NMR spectra were recorded on Bruker 300 MHz and 400 MHz instruments. HPLC-MS was performed on a Perkin Elmer instrument (API 100).

10

HPLC-systems from Merck-Hitachi (Hibar™ RT 250-4, Lichrosorb™ RP 18, 5.0 μm, 4.0 x 250 mm, gradient elution, 20% to 80% acetonitrile in water within 30 min, 1.0 mL/min, detection at 254 nm) and Waters (Symmetry™, C₁₈, 3.5 μm, 3.0 x 150 mm, gradient elution, 5% to 90% acetonitrile in water within 15 min, 1.0 mL/min, detection at 214 nm) were used.

15

Furthermore, where stated the following HPLC method h8 was used:

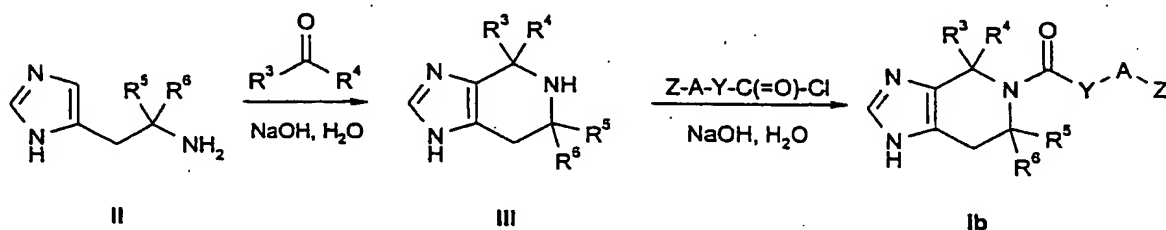
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The reverse phase analysis was performed using UV detections at 214, 254, 276 and 301 nm on a 218TP54 4.6 mm x 150 mm C-18 silica column, which was eluted at 1 mL/min at 42 °C. The column was equilibrated with 5% acetonitrile, 85% water and 10% of a solution of 0.5% trifluoroacetic acid in water and eluted by a linear gradient from 5% acetonitrile, 85% water and 10% of a solution of 0.5% trifluoroacetic acid to 90% acetonitrile and 10% of a solution of 0.5% trifluoroacetic acid over 15 min.

Where stated the following general procedures were used:

25

General Procedure A:



To a solution of the dihydrochloride of the amine II (10.0 mmol) in water (5 mL) an aqueous sodium hydroxide solution (12 N, 4.2 mL, 50.4 mmol), methanol (35 mL) and the carbonyl compound R^3R^4CO (25.0 mmol) were added. The resulting mixture was refluxed overnight, water (15 mL) was added, methanol was evaporated under reduced pressure and the residue was diluted with water to a volume of approximately 25 mL. The resulting mixture was washed with ether (2 x 50 mL, removal of excess ketone) and then, while stirring vigorously, the acyl halide (Z-A-Y-CO-Cl, 11.5 mmol) was added portionwise. After stirring for 10 min the mixture was extracted with DCM (2 x 100 mL). The combined organic phases were washed with water (25 mL), dried ($MgSO_4$) and concentrated. The remaining oil was redissolved in ethyl acetate (100 mL) and a solution of oxalic acid (0.45 g, 5.0 mmol) in ethyl acetate (25 mL) was added. After stirring for 30 min the precipitate was filtered off and dried under reduced pressure. Alternatively, the crude product Ib could be purified by column chromatography (silica gel, gradient elution with heptane/ethyl acetate/methanol).

15

General Procedure B:

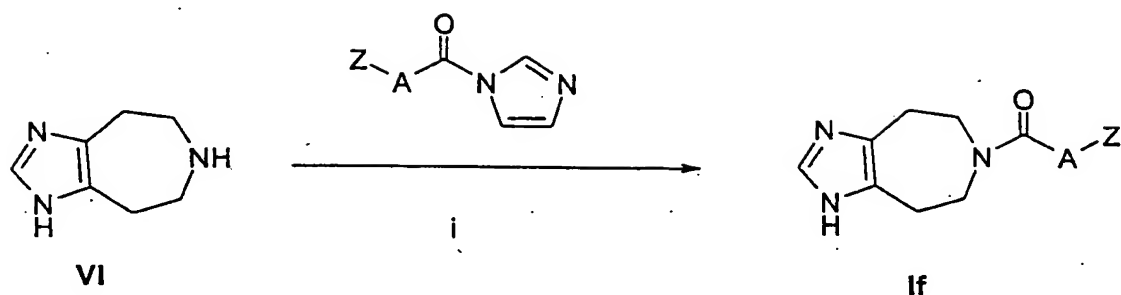
A mixture of the dihydrochloride of the amine II (95 mmol), water (200 mL), and the carbonyl compound R^3R^4CO (133 mmol) was refluxed until no more amine II could be detected (HPLC). The mixture was then concentrated to dryness and the crude product III was purified by recrystallization.

20

The purified amine III was then acylated as in general procedure A or by any other, conventional method.

25

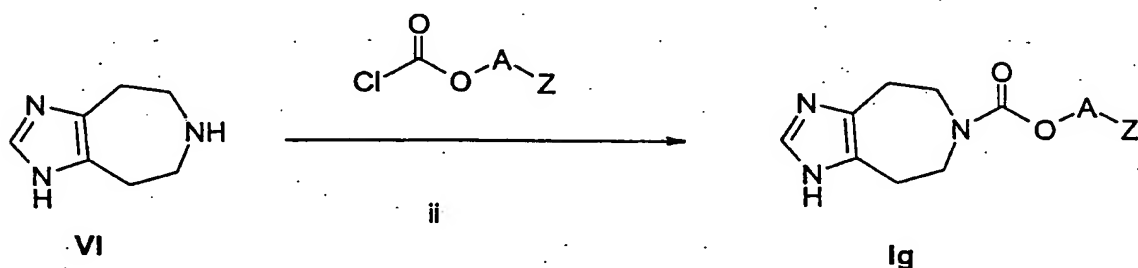
General Procedure C:



- 5 i: Z-A-COOH, carbonylimidazol, CH₃CN, 75 °C

To 0.3 mmol of the corresponding acid in CH₃CN (1 mL) was added 0.31 mmol *N,N*-carbonyldiimidazol in portions. The reaction mixture was stirred for 30 min. at room temperature and for 2 h at 75 °C. Then, it was cooled to room temperature and 0.25
 10 mmol of **VI** were added. The reaction mixture was heated for 2-5 h at 75 °C, cooled to room temperature and evaporated to dryness. The residue was chromatographed on SiO₂ with CH₂Cl₂/MeOH (10:1 to 4:1) to yield a compound of the general formula **If** as a white amorphous solid.

15 General Procedure D:



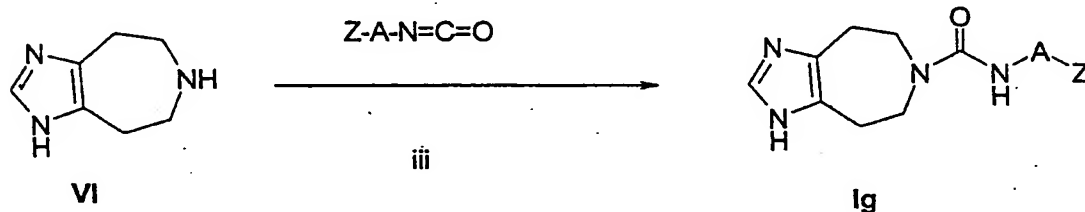
- ii: Z-A-OH, phosgene solution (1M in toluene), THF

20

To a solution of 0.3 mmol of the corresponding alcohol Z-A-OH in THF (1 mL) was added at 4 °C 0.16 mL phosgene solution (1.9 M in toluene). The reaction mixture was stirred for 3 h at room temperature and evaporated to dryness. The residue was

dissolved in CH₃CN (0.3 mL) and added to a solution of 0.25 mmol VI in CH₃CN (1 mL) at room temperature and stirred for 24 h at room temperature to 50°C. The reaction mixture was evaporated to dryness and the residue chromatographed on SiO₂ with CH₂Cl₂/MeOH (10:1 to 4:1) to yield a compound of the general formula Ig as a white amorphous solid.

General Procedure E:

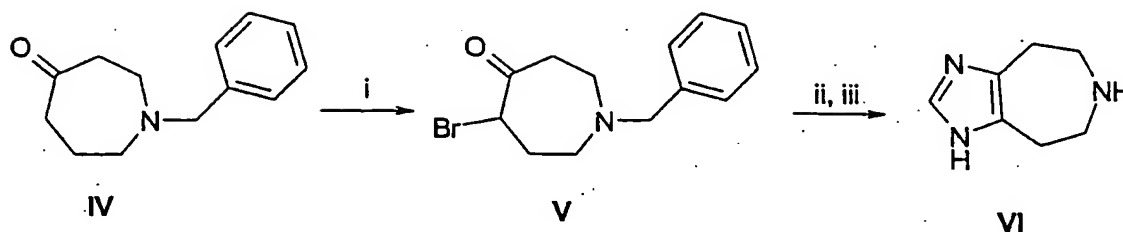


iii: Z-A-NH₂, triphosgene, Hünig's base, CH₃CN

To a solution of 0.3 mmol amine or aniline Z-A-NH₂ in CH₃CN (1 mL) was added at 4 °C 0.11 mmol triphosgene and 0.9 mmol Hünig's base to yield a clear solution, which was stirred for 30 min. at room temperature and for 2 h at 75 °C. Building block VI (0.25 mmol) was added at room temperature and the reaction mixture stirred for 24 h at 25-50 °C, cooled to room temperature and evaporated to dryness. The residue was chromatographed on SiO₂ with CH₂Cl₂/MeOH (10:1 to 4:1) to yield a compound of the general formula Ig as a white amorphous solid.

The key building blocks VI used in the above General Procedures C, D and E were synthesized as shown in Scheme 1. The synthesis of the non-commercial building blocks used is described in Scheme 2.

Scheme 1



5 i: Br₂, HBr-AcOH, AcOH

ii: formamidine x AcOH, EtOH, 80 °C; then aq. NaHCO₃ and extraction with CHCl₃ and chromatography with CH₂Cl₂/MeOH (9:1)

iii: Pd/C, EtOH

10 Synthesis of 4,5,7,8-tetrahydro-1H,6H-imidazo[4,5-d]azepine VI from 1-benzylhexahydroazepin-4-one hydrochloride IV

Step (i): 1-Benzyl-5 bromohexahydroazepin-4-one hydrobromide V

175 g of (0.732 mol) 1-benzylhexahydroazepin-4-one hydrochloride IV are dissolved
15 in 500 mL acetic acid. Upon addition of 100 mL of a saturated solution (30%) of hydrobromic acid in acetic acid, 37 mL (0.732 mol) of bromine are added dropwise at room temperature and with efficient stirring, whereby the brown colour of bromine disappears.

20 After completion of the addition the reaction mixture is concentrated on a rotavapor at a bath temperature of 35°C.

The resulting oily residue is triturated with ether and the ether layer decanted. Then 250 mL of ethyl acetate are added. The mixture is stirred and heated on a steam
25 bath until crystallization occurs. After cooling the ethyl acetate is removed by decantation and heated a second time with fresh ethyl acetate. Thereafter the crystalline material is collected by filtration and dried *in vacuo*.

Yield: 217.8 g (82%), m.p. 148-150°C.

Step (ii): 6-Benzyl-4,5,7,8-tetrahydro-1*H*,6*H*-imidazo[4,5-*d*]azepine

A solution of sodium ethanolate is prepared by dissolving 1.4 g (60 mmol) of sodium in 150 mL of dry ethanol. Then 4.8 g (60 mmol) of formamidine hydrochloride and 7.3 g (20 mmol) of 1-benzyl-5-bromohexahydroazepin-4-one hydrobromide as well as 80 mL chloroform are added successively. After keeping at reflux for about 8 hours the mixture is cooled and treated with a solution of 40 mmol of sodium hydroxide in dry methanol. The reaction mixture is concentrated on a rotavapor and the residue purified by column chromatography on silicagel with chloroform/methanol 9:1 as eluent.

Upon evaporation of the respective fractions the product is triturated with ethyl ether and collected by filtration.

Yield: 1.1 g (24.4%).

Step (iii): 4,5,7,8-Tetrahydro-1*H*,6*H*-imidazo[4,5-*d*]azepine

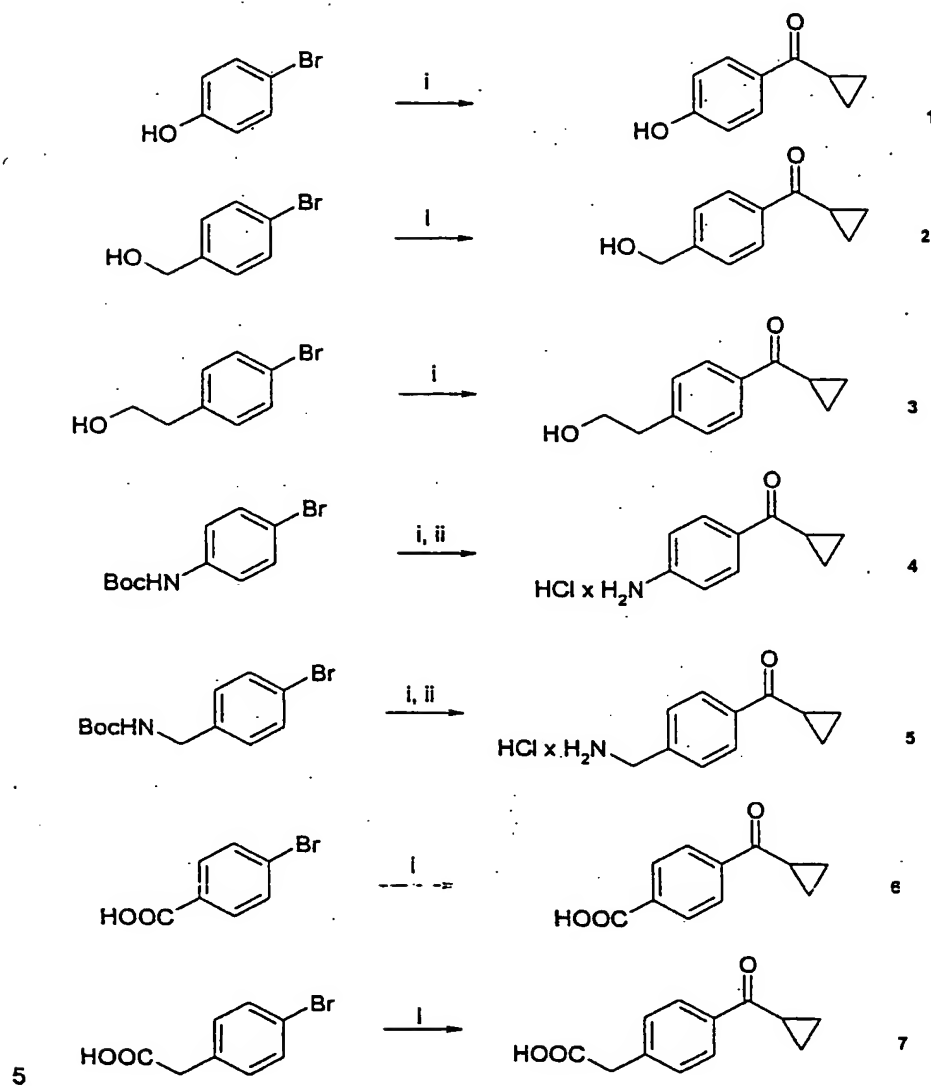
25.4 mmol of 6-benzyl-4,5,7,8-tetrahydro-1*H*-imidazo[4,5-*d*]azepine are dissolved in 180 ml ethanol and upon addition of 1.5 g palladium on charcoal treated with hydrogen at a pressure of 5 bar.

After removal of the catalyst the filtrate is evaporated on a rotavapor and the residue crystallized from acetonitrile.

Yield of 4,5,7,8-tetrahydro-1*H*,6*H*-imidazo[4,5-*d*]azepine = 59.3%.

The synthesis of the non-commercial building blocks 1-7 are described in Scheme 2.

Scheme 2



i: MeLi (1.6 M in Et₂O, 1.1 equiv.), THF, 0 °C; then tertiary BuLi (1.5 M in pentane, 2.2 equiv.), -78 °C, 1 h; then Weinreb amide of cyclopropane carboxylic acid, 0 °C
 ii: 4 N HCl in dioxane

To a stirred solution of a commercially available bromide (10 mmol) in THF (40 mL) was added at 4 °C MeLi solution (6.9 ml, 1.1 equiv., 1.6 M in Et₂O). The reaction mixture was stirred for 30 min. at 4 °C, cooled to -78 °C followed by addition of tertiary BuLi solution (14.7 mL, 2.2 equiv., 1.5 M in pentane). The reaction mixture was stirred for 1 h at -78 °C followed by addition of the Weinreb amide of cyclopropane carboxylic acid (15.0 mmol). The reaction mixture was allowed to warm to 0 °C overnight and poured onto ice, 0.5 N HCl solution and EtOAc. The organic layer was washed with saturated brine, dried (MgSO₄) and evaporated and the residue chromatographed on SiO₂.

Building blocks:

1: ¹H NMR (300 MHz, DMSO-*d*₆): δ 10.32 (br. s, 1H); 7.91 (d, *J* = 8.8, 2H); 6.84 (d, *J* = 8.8, 2H); 2.77 (m, 1H); 0.96-0.93 (m, 4H).

2: ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.99 (d, *J* = 8.2, 2H); 7.46 (d, *J* = 8.4, 2H); 5.35 (t, *J* = 5.7, 1H); 4.57 (d, *J* = 5.7, 2H); 2.87 (m, 1H); 1.03-1.00 (m, 4H).

3: ¹H NMR (300 MHz, CDCl₃): δ 7.94 (d, *J* = 8.3, 2H); 7.32 (d, *J* = 8.4, 2H); 3.87 (t, *J* = 6.6, 2H); 2.92 (t, *J* = 6.6, 2H); 2.65 (m, 2H); 1.27-1.19 (m, 2 H); 1.05-0.99 (m, 2H).

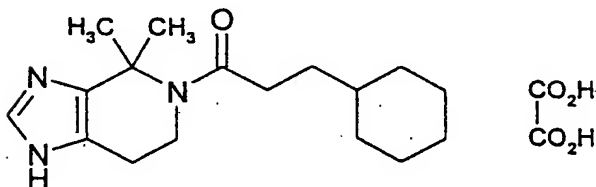
4: ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.18 (br. s, 3H); 7.85 (d, *J* = 8.8, 2H); 6.82 (d, *J* = 8.8, 2H); 2.74 (m, 1H); 0.92-0.88 (m, 4H).

5: ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.56 (br. s, 3 H); 8.06 (d, *J* = 8.4, 2H); 7.64 (d, *J* = 8.6, 2H); 4.10 (s, 2H); 2.90 (m, 1H); 1.06-1.01 (m, 4H).

6: ¹H NMR (300 MHz, CDCl₃): δ 8.22 (d, *J* = 8.6, 2H); 8.09 (d, *J* = 8.4, 2H); 2.69 (m, 1H); 1.30 (m, 2H); 1.12 (m, 2H).

7: could not be obtained in pure form.

Example 1: 5-(3-Cyclohexylpropanoyl)-4,4-dimethyl-4,5,6,7-tetrahydroimidazo[4,5-c]-pyridine oxalic acid salt



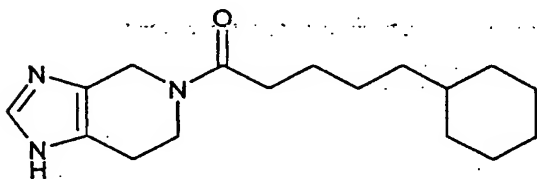
5

Following the General Procedure A using histamine dihydrochloride (1.84 g, 10.0 mmol), acetone (4.0 mL) and 3-cyclohexylpropanoyl chloride (2.0 g, 11.5 mmol) 0.80 g (21%) of the title amide was obtained as oxalic acid salt.

10 HPLC (214 nm): elution at 18.59 min. LC-MS: Calcd. for MH⁺: 290; found: 290.

¹H NMR (400 MHz, DMSO-*d*₆, two rotamers, 6:4): δ 0.80-0.95 (m, 2H), 1.05-1.28 (m, 4H), 1.35-1.76 (m, 13H), 2.38 (m, 1.2H), 2.64 (t, *J* = 5 Hz, 1.2H), 2.89 (t, *J* = 5 Hz, 0.8H), 3.01 (t, *J* = 7 Hz, 0.8H), 3.54 (t, *J* = 5 Hz, 0.8H), 3.58 (t, *J* = 5 Hz, 1.2H), 8.25
15 (s, 0.6H), 8.34 (s, 0.4H).

Example 2: 5-(5-Cyclohexylpentanoyl)-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine



20

To a solution of 5-cyclohexylpentanoic acid (0.94 g, 5.10 mmol) in DCM (4 mL) carbonyldiimidazole (0.83 g, 5.12 mmol) was added. The resulting mixture was stirred at room temperature for 16 h and then added to a solution of 4,5,6,7-tetrahydroimidazo[4,5-c]pyridine (5.10 mmol) in DCM (4 mL). After 2.5 h DCM (50 mL) was
25 added and the mixture was washed with water (3 x 15 mL). The organic layer was then dried (MgSO₄) and concentrated. The crude product was purified by column

chromatography (silica gel, ethyl acetate/methanol 9:1) whereby 0.35 g (24%) of the title amide was obtained as an oil.

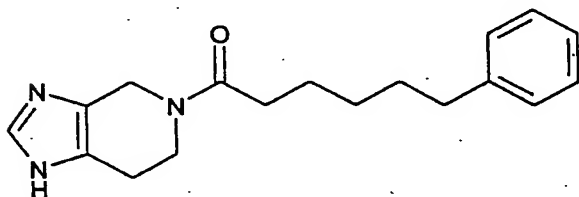
HPLC (214 nm): elution at 20.74 min. LC-MS: Calcd. for MH^+ : 290; found: 290.

5

1H NMR (400 MHz, $DMSO-d_6$, two rotamers, 1:1): δ 0.70-0.80 (m, 2H), 1.05-1.34 (m, 8H), 1.43-1.52 (m, 2H), 1.55-1.71 (m, 5H), 2.36 (m, 2H), 2.52 (t, $J = 5$ Hz, 1H), 2.62 (t, $J = 5$ Hz, 1H), 3.68 (t, $J = 5$ Hz, 1H), 3.74 (t, $J = 5$ Hz, 1H), 4.41 (s, 2H), 7.47 (s, 0.5H), 7.49 (s, 0.5H), 11.85 (s, br, 1H).

10

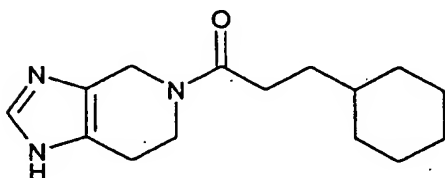
Example 3: 5-(6-Phenylhexanoyl)-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine



- 15 To a solution of carbonyldiimidazole (0.83 g, 5.12 mmol) in DCM (8 mL) 6-phenylhexanoic acid (0.98 g, 5.10 mmol) was added dropwise. The mixture was stirred at room temperature for 20 h, and then a solution of 4,5,6,7-tetrahydroimidazo[4,5-c]pyridine (5.10 mmol) in DMF (1 mL) and DCM (1 mL) was added. After stirring for four days DCM (100 mL) was added and the mixture was washed with water (15 mL)
- 20 and dried ($MgSO_4$). Concentration and column chromatography (silica gel, ethyl acetate/methanol 9:1) gave 0.80 g (53%) of the title amide as an oil.

1H NMR (400 MHz, $DMSO-d_6$, two rotamers, 1:1): δ 1.22-1.38 (m, 2H), 1.46-1.64 (m, 4H), 2.38 (m, 2H), 2.45-2.68 (m, 6H), 3.68 (t, $J = 5$ Hz, 1H), 3.72 (t, $J = 5$ Hz, 1H),

25 4.41 (s, 2H), 7.14-7.29 (m, 5H), 7.48 (s, 0.5H), 7.50 (s, 0.5H), 11.90 (s, br, 1H).

Example 4: 5-(3-Cyclohexylpropanoyl)-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine

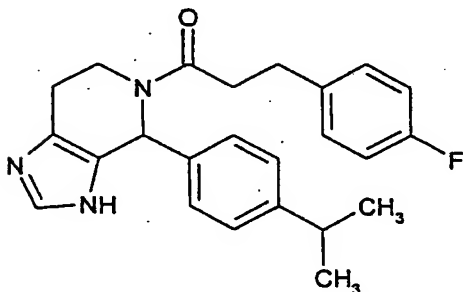
- 5 To a solution of carbonyldiimidazole (0.83 g, 5.12 mmol) in DCM (8 mL) 3-cyclohexylpropionic acid (0.80 g, 5.10 mmol) was added dropwise. The mixture was stirred at room temperature for 20 h, and then a solution of 4,5,6,7-tetrahydroimidazo[4,5-c]pyridine (5.10 mmol) in DMF (1 mL) and DCM (1 mL) was added. After stirring for four days DCM (100 mL) was added and the mixture was washed with water (15 mL)
- 10 and dried (MgSO₄). Concentration and column chromatography (silica gel, ethyl acetate/methanol 9:1) gave 0.66 g (50%) of the title amide as an oil.

¹H NMR (400 MHz, DMSO-*d*₆, two rotamers, 1:1): δ 0.80-0.95 (m, 2H), 1.05-1.30 (m, 4H), 1.90 (m, 2H), 1.56-1.75 (m, 5H), 2.39 (m, 2H), 2.52 (t, *J* = 5 Hz, 1H), 2.61 (t, *J* = 5 Hz, 1H), 3.69 (t, *J* = 5 Hz, 1H), 3.72 (t, *J* = 5 Hz, 1H), 4.42 (s, 2H), 7.51 (s, 0.5H), 7.53 (s, 0.5H), 11.90 (s, br, 1H).

15

Example 5: 5-[3-(4-Fluorophenyl)propanoyl]-4-(4-isopropylphenyl)-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine

20



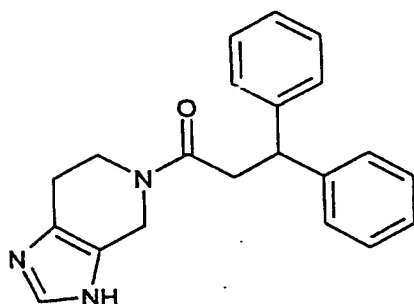
A mixture of histamine dihydrochloride (1.85 g, 10.0 mmol), water (10 mL), potassium hydroxide (1.72 g, 30.0 mmol), ethanol (25 mL) and 4-isopropylbenzaldehyde (1.62

g, 10.91 mmol) was heated to reflux for 1.5 h. Ethanol was evaporated and the residue was diluted with water (40 mL). Extraction (5 x 25 mL DCM), washing of the combined extracts (2 x 50 mL brine) and drying (MgSO_4) yielded 2.29 g (87%) of crude 4-(4-isopropylphenyl)-4,5,6,7-tetrahydro-imidazo[4,5-c]pyridine, which was used for the next synthetic step without further purification. This amine (0.48 g, 1.99 mmol) was dissolved in DCM (5 mL) and added to a 30 min old mixture of 3-(4-fluorophenyl)propionic acid (0.31 g, 1.84 mmol), HOBt (0.27 g, 1.20 mmol) and EDC (0.42 g, 2.19 mmol) in DCM (10 mL). After 18 h the mixture was washed with water (50 mL), dried (MgSO_4) and concentrated. The crude product was purified by column chromatography (silica gel, gradient elution with DCM/methanol). 0.24 g (33%) of the title amide was obtained.

HPLC (214 nm): elution at 10.21 min. LC-MS: Calcd. for MH^+ : 392; found: 392.

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 1.18 (d, $J = 7$ Hz, 6H), 2.50-2.94 (m, 7H), 3.05 (m, 1H), 3.95 (m, 1H), 6.48 (s, br, 0.7H), 6.67 (s, br, 0.3H), 6.99-7.35 (m, 8H), 7.55 (s, 1H), 11.90 (s, 1H).

Example 6: 5-(3,3-Diphenylpropanoyl)-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine



To a suspension of 3,3-diphenylpropionic acid (14 mg, 0.06 mmol) and HOBt (9 mg, 0.07 mmol) in ethyl acetate (1.5 mL) a solution of EDC (12 mg, 0.06 mmol) in ethyl acetate (0.5 mL) was added. The resulting mixture was shaken for 20 min at room temperature and then 4,5,6,7-tetrahydroimidazo[4,5-c]pyridine dihydrochloride (12 mg, 0.06 mmol) and triethylamine (0.02 mL) were added. After shaking for 16 h the

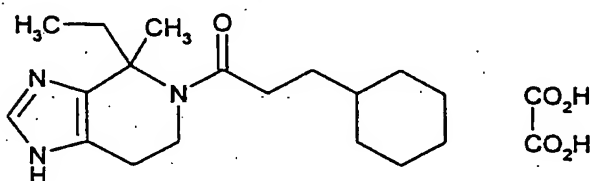
mixture was washed with brine (2 x 2 mL), and the organic phase was concentrated. 12 mg (60%) of the title amide was obtained.

HPLC (214 nm): elution at 8.71 min. LC-MS: Calcd. for MH^+ : 332; found: 332.

5

1H NMR (300 MHz, $CDCl_3$, two rotamers, 1:1): δ 2.55 (m, 2H), 3.15 (t, $J = 7$ Hz, 2H), 3.61 (t, $J = 5$ Hz, 1H), 3.80 (t, $J = 5$ Hz, 1H), 4.41 (s, 1H), 4.57 (s, 1H), 4.67 (m, 1H), 7.06-7.30 (m, 10H), 7.39 (s, 0.5H), 7.43 (s, 0.5H).

- 10 **Example 7:** 5-(3-Cyclohexylpropanoyl)-4-ethyl-4-methyl-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine oxalic acid salt



- 15 From histamine dihydrochloride (1.85 g, 10.0 mmol), 2-butanone (1.80 g, 25.0 mmol) and 3-cyclohexylpropanoyl chloride (2.0 g, 11.5 mmol) 0.60 g (15%) of the title oxalate was obtained using the General Procedure A.

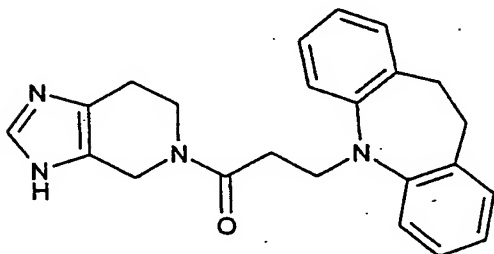
HPLC (214 nm): elution at 19.54 min. LC-MS: Calcd. for MH^+ : 304; found: 304.

20

1H NMR (400 MHz, $DMSO-d_6$, two rotamers, 2:1): δ 0.39 (t, $J = 7$ Hz, 2H), 0.79-0.93 (m, 2H), 0.95 (t, $J = 7$ Hz, 1H), 1.05-1.29 (m, 4H), 1.39 (m, 2H), 1.49 (s, 1H), 1.59 (s, 2H), 1.60-2.10 (m, 7H), 2.15-2.50 (m, 1H), 2.60-2.99 (m, 3H), 3.28-3.49 (m, 1.3H), 3.88 (m, 0.7H), 7.69 (s, 0.3H), 8.39 (s, 0.7H).

25

Example 8: 5-[3-(10,11-Dihydro-5*H*-dibenzo[b,f]azepin-5-yl)propanoyl]-4,5,6,7-tetrahydroimidazo[4,5-*c*]pyridine



5

Iminodibenzyl (50.0 g, 0.256 mol) was dissolved in DMF (700 mL), sodium hydride (12.3 g, 0.306 mol, 60% dispersion in oil) was slowly added in portions and the mixture was stirred at 50 °C for 2 h. Ethyl 3-bromopropionate (100 mL, 0.77 mol) was slowly added dropwise and the mixture was heated at reflux temperature overnight.

10 The mixture was cooled and evaporated. The residue was suspended in DCM (150 mL), filtered and the solvent was evaporated. The resulting residue was purified in portions by column chromatography (silica gel, DCM) to give 5.1 g (7%) of 3-(10,11-dihydro-5*H*-dibenzo[b,f]azepin-5-yl)propionic acid ethyl ester.

15 TLC: R_f = 0.69 (silica gel, DCM).

3-(10,11-Dihydro-5*H*-dibenzo[b,f]azepin-5-yl)propionic acid ethyl ester (1.41 g, 4.77 mmol) was dissolved in ethanol (30 mL) and a solution of sodium hydroxide (0.75 g, 18.8 mmol) in water (5 mL) was added. The mixture was stirred for 3.5 h. 1 N Hydrochloric acid (17 mL) was added and the mixture was extracted with DCM (2 x 25 mL).
20 The combined organic extracts were washed with brine (50 mL), dried (MgSO_4) and the solvent was evaporated to give 1.18 g (92%) of 3-(10,11-dihydro-5*H*-dibenzo[b,f]azepin-5-yl)propionic acid.

25 Carbonyldiimidazole (0.33 g, 2.1 mmol) was dissolved in DCM (5 mL) and 3-(10,11-dihydro-5*H*-dibenzo[b,f]azepin-5-yl)-1-propionic acid (0.56 g, 2.1 mmol) was added. The mixture was stirred at room temperature for 1.5 h under a nitrogen atmosphere. Simultaneously, sodium methoxide (0.8 mL of a 30% solution in water, 4.4 mmol)

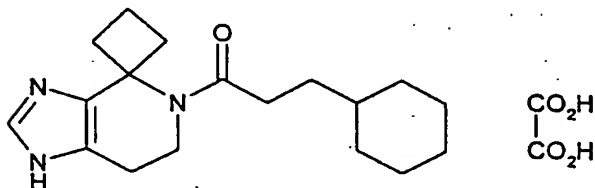
was added to a solution of 4,5,6,7-tetrahydroimidazo[4,5-c]pyridine dihydrochloride (0.43 g, 2.2 mmol) in methanol (5 mL). The mixture was stirred at room temperature for 1.5 h under a nitrogen atmosphere. The solvent was evaporated and the residue was stripped with DCM (6 mL). The above solution of the activated carboxylic acid
5 was added to the residue and the reaction mixture was stirred at room temperature overnight. Water (10 mL) was added followed by DCM (50 mL) and the phases were separated. The aqueous phase was extracted with DCM (20 mL) and the combined organic phases were dried (MgSO₄). After evaporation of the solvent, the residue was purified by column chromatography (silica gel, 150 mL, methanol/ ethyl acetate
10 1:5). Evaporation of the solvent afforded 0.41 g (52%) of the title compound as a solid.

TLC: R_f = 0.28 (silica gel, methanol/ethyl acetate 1:5). LC-MS: Calcd. for MH⁺: 373; found: 373.

15

¹H NMR (400 MHz, DMSO-*d*₆, two rotamers, 1:1): δ 2.49 (m, 1H), 2.60-2.72 (m, 3H), 3.07 (d, 4H), 3.47 (t, 1H), 3.86 (t, 1H), 4.08-4.20 (m, 2H), 4.22 (s, 1H), 4.62 (s, 1H), 6.90 (m, 2H), 7.01-7.16 (m, 6H), 7.40 (s, 0.5H), 7.45 (s, 0.5H).

20 **Example 9:** 5-(3-Cyclohexylpropanoyl)-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine-4-spirocyclobutane oxalic acid salt



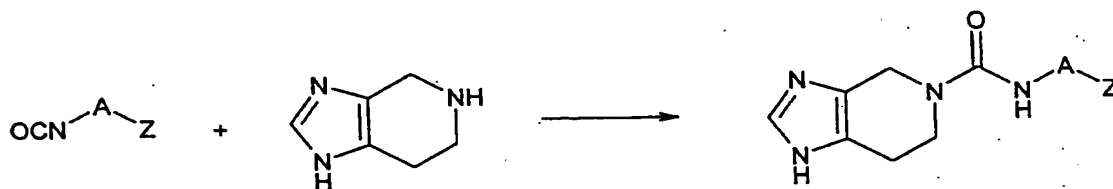
25 From histamine dihydrochloride (1.85 g, 10.0 mmol), cyclobutanone (1.75 g, 25.0 mmol) and 3-cyclohexylpropanoyl chloride (2.0 g, 11.5 mmol), 0.70 g (18%) of the title oxalate was obtained (General Procedure A).

HPLC (214 nm): elution at 19.40 min. LC-MS: Calcd. for MH⁺: 302; found: 302.

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 0.75-0.95 (m, 2H), 1.04-1.28 (m, 4H), 1.35 (q, $J = 7$ Hz, 2H), 1.50-2.70 (m, 11H), 3.63 (t, $J = 5$ Hz, 2H), 8.22 (s, br, 1H).

5 Example 10: Parallel Synthesis of Ureas

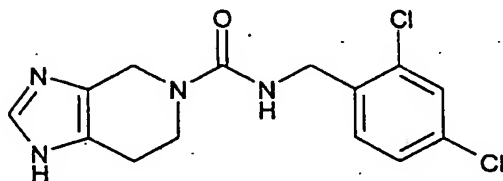
To each reactor of an array of 12 reactors, each containing a solution of 4,5,6,7-tetrahydroimidazo[4,5-c]pyridine dihydrochloride (0.07 mmol) in DMF (0.5 mL, containing 5% triethylamine) a solution of one isocyanate (0.9 equivalents) selected from 12 different isocyanates in 1,2-dichloroethane (0.2 mL) was added. The resulting mix-
 10 tures were shaken overnight at room temperature. Concentration under reduced pressure gave the corresponding ureas. Using this methodology the following ureas were prepared:



15

Example	Z-A-	MH ⁺ (calcd)	MH ⁺ (found)
10-001	2-(2-thienyl)ethyl	277	277
10-002	3,5-dimethyl-1,2-oxazol-4-yl	262	262
10-003	1-(1-naphthyl)ethyl	321	
10-004	(2-phenylcyclopropyl)	283	283
10-005	1-(4-bromophenyl)ethyl	350	
10-006	2-(trifluoromethyl)phenyl	311	311
10-007	2-phenylethyl	271	271
10-008	4-(trifluoromethyl)phenyl	311	311
10-009	3-cyanophenyl	268	268
10-010	4-cyanophenyl	268	268
10-011	n-octyl	279	279

Example 11: 5-(2,4-Dichlorobenzylaminocarbonyl)-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine



5

To a mixture of 4,5,6,7-tetrahydroimidazo[4,5-c]pyridine dihydrochloride (0.50 g, 2.55 mmol), ethanol (10 mL) and triethylamine (1.10 mL, 7.89 mmol), 2,4-dichlorobenzyl isocyanate (0.52 g, 2.57 mmol) was added. The resulting mixture was stirred at room temperature for 16 h and then concentrated under reduced pressure. The residue was distributed between water (20 mL) and ethyl acetate (75 mL). The organic phase was washed with water (10 mL) and brine (10 mL), dried (MgSO₄) and concentrated under reduced pressure. The residue was triturated in diethylether (50 mL) and the crude product was filtered off. Recrystallization from acetone (25 mL) gave 0.30 g (37%) of the title urea as a colourless solid.

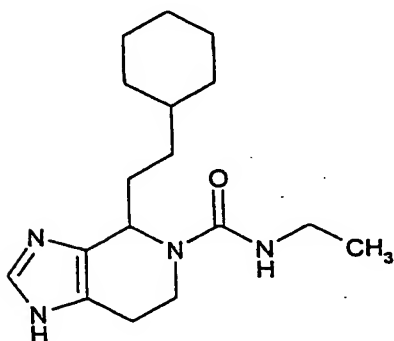
15

HPLC (214 nm): elution at 7.97 min. LC-MS: Calcd. for MH⁺: 325; found: 325.

¹H NMR (400 MHz, DMSO-*d*₆): δ 2.56 (s, br, 2H), 3.65 (t, *J* = 6 Hz, 2H), 4.29 (d, *J* = 6 Hz, 2H), 4.34 (s, 2H), 7.20 (s, br, 1H), 7.29 (d, *J* = 8 Hz, 1H), 7.39 (dd, *J* = 8, 1 Hz, 1H), 7.47 (s, 1H), 7.56 (d, *J* = 1 Hz, 1H), 11.79 (s, br, 1H).

20

Example 12: 4-(2-Cyclohexylethyl)-5-(ethylaminocarbonyl)-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine



5

To a solution of histamine dihydrochloride (1.84 g, 10.0 mmol) in water (5 mL) methanol (40 mL) was added. To this stirred mixture an aqueous 12 N sodium hydroxide solution (4.2 mL, 50.4 mmol) and 3-(cyclohexyl)propionaldehyde (3.5 g, 25 mmol) were added. The resulting mixture was heated at reflux temperature for 20 h.

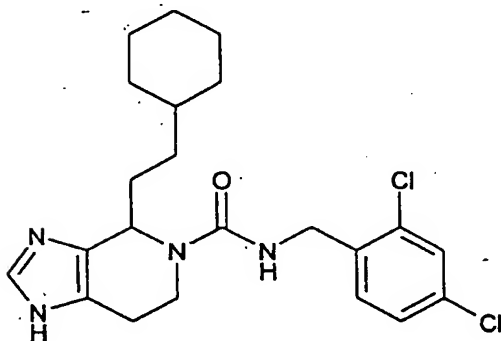
10 Concentrated hydrochloric acid was added until pH 1 and the mixture was diluted with water (100 mL). The mixture was washed with diethyl ether (3 x 25 mL) and the aqueous solution was concentrated under reduced pressure. The residue was suspended in methanol (150 mL) and the suspension was filtered. The filtrate was concentrated under reduced pressure to give a residue which was treated with warm
15 ethanol (75 mL). The resulting mixture was filtered and the filtrate was concentrated under reduced pressure to a volume of approximately 10 mL. Acetone (50 mL) was added and the mixture was left for crystallization. The solid was isolated by filtration and dried under reduced pressure to give 2.4 g of a solid which was dissolved in water (10 mL). While stirring, an aqueous 1 N sodium hydroxide solution was added until pH 11-12. The resulting mixture was extracted with ethyl acetate (200 mL), the extracts were dried (MgSO₄) and the solvent was evaporated under reduced pressure.
20 This afforded 1.25 g of 4-(2-cyclohexylethyl)-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine.

To a solution of the above amine (0.45 g, 1.9 mmol) in ethanol (10 mL), triethylamine
25 (0.2 g, 1.9 mmol) and ethyl isocyanate (0.14 g, 1.9 mmol) were added. The mixture was stirred overnight at room temperature and then concentrated under reduced

pressure. The crude product was purified by column chromatography (silica gel, elution with ethyl acetate/methanol 9:1). This afforded 0.14 g (24% calculated from the amine) of the title compound as a solid.

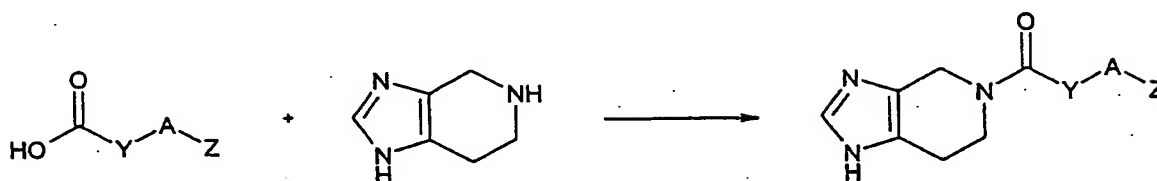
- 5 M.p. 210-212 °C. ¹H NMR (400 MHz, DMSO-*d*₆): δ 0.85 (m, 2H), 1.00 (t, 3H), 1.05-1.45 (m, 6H), 1.50-1.75 (m, 7H), 2.35 (m, 1H), 2.55 (m, 1H), 3.03 (m, 3H), 4.10 (m, br, 1H), 4.85 (m, br, 1H), 6.38 (s, br, 1H), 7.40 (s, 1H), 11.68 (s, br, 1H).

Example 13: 4-(2-Cyclohexylethyl)-5-(2,4-dichlorobenzylaminocarbonyl)-4,5,6,7-tetrahydroimidazo[4,5-*c*]pyridine
10



To a solution of 4-(2-cyclohexylethyl)-4,5,6,7-tetrahydroimidazo[4,5-*c*]pyridine (0.47
15 g, 2.0 mmol, prepared as described in Example 13) in ethanol (10 mL), triethylamine (0.28 ml, 2.0 mmol) and 2,4-dichlorobenzyl isocyanate (0.41 g, 2.0 mmol) were added dropwise. The mixture was stirred overnight at room temperature and then concentrated under reduced pressure. The residue was re-evaporated with acetone and then dissolved in acetone (15 mL) and left for crystallization. The solid was iso-
20 lated by filtration, washed with acetone and dried. This afforded 0.60 g (69%) of the title compound as a solid.

M.p. 185-187 °C. ¹H NMR (400 MHz, DMSO-*d*₆): δ 0.85 (m, 2H), 1.05-1.45 (m, 6H), 1.52-1.70 (m, 7H), 2.42 (m, 1H), 2.60 (m, 1H), 3.09 (m, 1H), 4.18 (m, br, 1H), 4.28
25 (m, 2H), 4.96 (m, br, 1H), 7.10 (t, br, 1H), 7.28 (d, 1H), 7.38 (dd, 1H), 7.43 (s, 1H), 7.55 (d, 1H), 11.75 (s, br, 1H).

Example 14: Parallel Synthesis of Carboxamides

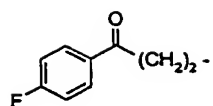
5

To each reactor in an array of six, a suspension of HOBt (7.4 mg, 55 μ mol) in a mixture of acetonitrile, 1,2-dichloroethane, NMP and DMSO (250 μ L) was added. Then a suspension of EDC (11.5 mg, 60 μ mol) in a mixture of acetonitrile, 1,2-dichloroethane, NMP and DMSO (250 μ L) was added to each reactor. To each reactor a carboxylic acid (50 μ mol, Z-A-Y- as listed below) dissolved in 1,2-dichloroethane (3 mL) was added and the array was shaken for 15 min. To each reactor 4,5,6,7-tetrahydroimidazo[4,5-c]pyridine (60 μ mol, prepared according to General Procedure B) dissolved in a mixture of acetonitrile (250 μ L) and triethylamine (210 μ L, 300 μ mol) was added and the array was shaken overnight. 1,2-Dichloroethane (1 mL) was added to each reactor and the array was shaken for 2 h. A 0.3 N hydrochloric acid solution (500 μ L) was added to each reactor and the array was shaken for 2 h. The lower phase of each reactor was isolated with a pipette and concentrated under reduced pressure. This afforded the following six amides, identified by their MH^+ (LC-MS):

20

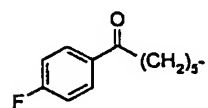
Example	Z-A-Y-	MH^+ (calcd)	MH^+ (found)
14-001		262	262
14-002		248	248
14-003		234	

14-004



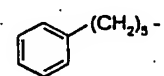
302

14-005



326

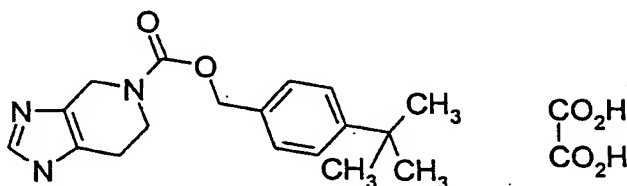
14-006



298

298

Example 15: 4,5,6,7-Tetrahydroimidazo[4,5-c]pyridine-5-carboxylic acid 4-*tert*-butylbenzyl ester oxalate



5

To a solution of 4-*tert*-butylbenzyl alcohol (1.97 g, 12 mmol) in DCM (30 mL) was added pyridine (1.3 mL) and then a solution of 4-nitrophenyl chloroformate (1.57 g, 7.8 mmol) in DCM (20 mL). The mixture was stirred at room temperature for 1 h, concentrated under reduced pressure, and to the residue was added a mixture of of
10 4,5,6,7-tetrahydroimidazo[4,5-c]pyridine (1.5 g, 7 mmol), methanol (3.3 mL), DMF (30 mL), and diisopropylethylamine (4.1 mL). The resulting mixture was stirred at room temperature overnight and concentrated under reduced pressure. The residue was distributed between water and ethyl acetate, phases were separated, and the organic layer was washed with water, dried (MgSO₄), and filtered. A solution of oxalic acid
15 (0.63 g) in ethyl acetate was added to the filtrate and the mixture was allowed to stand for 24 h. Filtration yielded the title compound as colourless solid.

20

¹H NMR (400 MHz, DMSO-*d*₆) δ 1.28 (s, 9H), 2.65 (m, 2H), 3.69 (t, *J* = 5 Hz, 2H), 4.46 (s, 2H), 5.08 (s, 2H), 7.31 (d, *J* = 8 Hz, 2H), 7.39 (d, *J* = 8 Hz, 2H), 8.13 (m, 1H).

(C₁₈H₂₃N₃O₂, C₂H₂O₄); calcd. 59.54C 6.25H 10.42N; found 59.66C 6.28H 10.35N.

The compound was prepared from 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-c]pyridine and 4-(*tert*-butyl)benzyl alcohol.

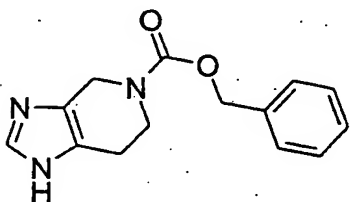
25

¹H NMR (400 MHz, DMSO-*d*₆) δ 1.28 (s, 9H), 2.65 (m, 2H), 3.69 (t, *J* = 5 Hz, 2H), 4.46 (s, 2H), 5.08 (s, 2H), 7.31 (d, *J* = 8 Hz, 2H), 7.39 (d, *J* = 8 Hz, 2H), 8.13 (m, 1H).

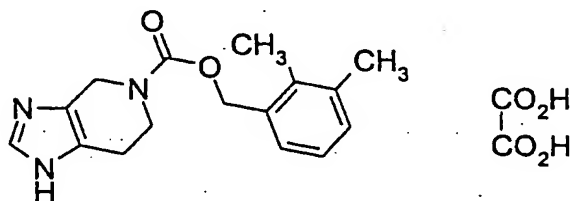
(C₁₈H₂₃N₃O₂, C₂H₂O₄); calcd. 59.54C 6.25H 10.42N; found 59.66C 6.28H 10.35N.

Using the same procedure as described for the above example the following compounds were prepared:

- 5 **Example 16:** 1,4,6,7-Tetrahydro-Imidazo[4,5-c]pyridine-5-carboxylic acid benzyl ester



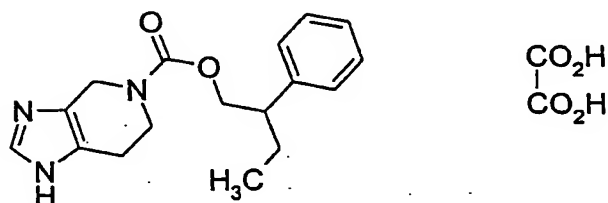
- 10 **Example 17:** 4,5,6,7-Tetrahydroimidazo[4,5-c]pyridine-5-carboxylic acid 2,3-dimethylbenzyl ester oxalate



- 15 The compound was prepared from 4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine and 2,3-dimethylbenzyl alcohol.

^1H NMR (400 MHz, DMSO- d_6) δ 2.19 (s, 3H), 2.27 (s, 3H), 2.63 (m, 2H), 3.70 (t, J = 6 Hz, 2H), 4.46 (s, 2H), 5.12 (s, 2H), 7.04–7.18 (m, 3H), 8.15 (s, br, 1H).

Example 18: 4,5,6,7-Tetrahydroimidazo[4,5-c]pyridine-5-carboxylic acid 2-phenyl-butyl ester oxalate



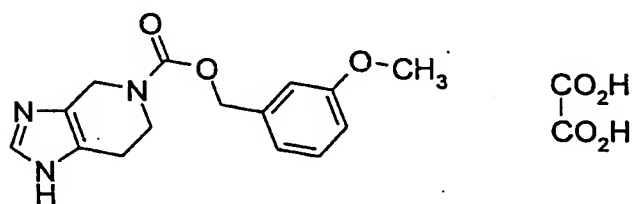
5

The compound was prepared from 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-c]pyridine and 2-phenyl-1-butanol oxalate.

M.p. 154-156 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.76 (t, *J* = 7 Hz, 3H), 1.53–1.66 (m, 1H), 1.70–1.80 (m, 1H), 2.40–2.63 (m, 2H), 2.82 (m, 1H), 3.48–3.65 (m, 2H), 4.11–4.22 (m, 2H), 4.25–4.40 (m, 2H), 7.18–7.34 (m, 5H), 8.09 (s, 1H).

Calcd. 58.60C 5.95H 10.79N; found 58.89C 5.93H 10.63N.

Example 19: 4,5,6,7-Tetrahydroimidazo[4,5-c]pyridine-5-carboxylic acid 3-methoxy-benzyl ester oxalate

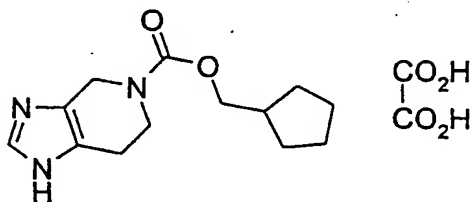


The compound was prepared from 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-c]pyridine and 2-phenyl-1-butanol oxalate.

M.p. 163-165 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.65 (t, *J* = 5 Hz, 2H), 3.69–3.75 (m, 5H), 4.48 (m, 2H), 5.09 (s, 2H), 6.87–6.95 (m, 3H), 7.29 (t, *J* = 8 Hz, 1H), 8.12 (s, 1H).

(C₁₅H₁₇N₃O₃, C₂H₂O₄); calcd. 54.11C 5.08H 11.14N; found 53.90C 5.04H 11.09N.

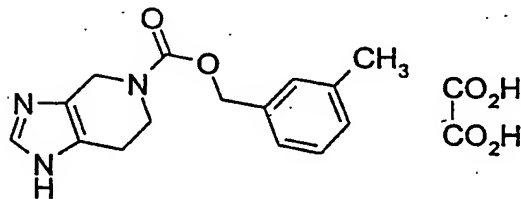
Example 20: 4,5,6,7-Tetrahydroimidazo[4,5-c]pyridine-5-carboxylic acid cyclopentyl-methyl ester oxalate



The compound was prepared from 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine and cyclopentylmethanol.

¹H NMR (400 MHz, DMSO-*d*₆) δ 1.22 (m, 2H), 1.45–1.61 (m, 4H), 1.62–1.75 (m, 2H), 2.16 (sept, *J* = 7 Hz, 1H), 2.63 (m, 2H), 3.68 (t, *J* = 5 Hz, 2H), 3.92 (d, *J* = 7 Hz, 2H), 4.44 (s, 2H), 8.16 (s, 1H).

Example 21: 4,5,6,7-Tetrahydroimidazo[4,5-*c*]pyridine-5-carboxylic acid 3-methylbenzyl ester oxalate

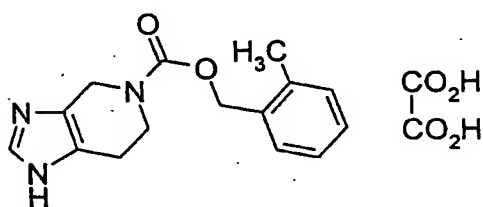


The compound was prepared from 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine and 3-methylbenzyl alcohol.

M.p. 169-171 °C. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 2.31 (s, 3H), 2.65 (m, 2H), 3.70 (m, 2H), 4.47 (s, 2H), 5.08 (s, 2H), 7.11–7.19 (m, 3H), 7.26 (t, $J = 8$ Hz, 1H), 8.15 (s, 1H).

5 (C₁₅H₁₇N₃O₂, C₂H₂O₄); calcd. 56.51C 5.30H 11.63N; found 56.74C 5.29H 11.63N.

Example 22: 4,5,6,7-Tetrahydroimidazo[4,5-c]pyridine-5-carboxylic acid 2-methylbenzyl ester oxalate



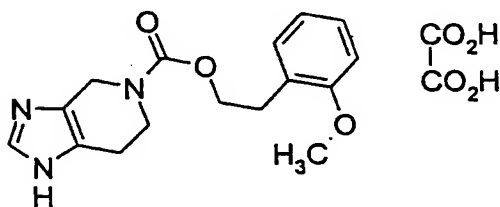
The compound was prepared from 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine and 2-methylbenzyl alcohol.

15 M.p. 158-160 °C. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 2.31 (s, 3H), 2.64 (s, 2H), 3.69 (t, $J = 5$ Hz, 2H), 4.46 (s, 2H), 5.12 (s, 2H), 7.15–7.26 (m, 3H), 7.31 (d, $J = 8$ Hz, 1H), 8.14 (s, 1H).

Calcd. 56.51C 5.30H 11.63N; found 56.38C 5.27H 11.43N.

20

Example 23: 4,5,6,7-Tetrahydroimidazo[4,5-*c*]pyridine-5-carboxylic acid 2-(2-methoxyphenyl)ethyl ester oxalate

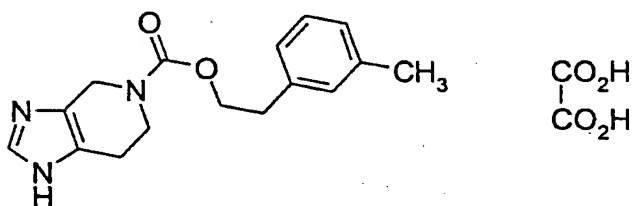


The compound was prepared from 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine and 2-(2-methoxyphenyl)-1-ethanol.

M.p. 165-167 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.53–2.63 (m, 2H), 2.88 (t, *J* = 5 Hz, 2H), 3.61 (s, br, 2H), 3.77 (s, 3H), 4.19 (t, *J* = 7 Hz, 2H), 4.39 (s, br, 2H), 6.85 (s, br, 1H), 6.95 (d, *J* = 8 Hz, 1H), 7.10–7.24 (m, 2H), 8.15 (s, 1H).

Calcd. 55.24C 5.41H 10.74N; found 55.39C 5.39H 10.62N.

- 10 **Example 24:** 4,5,6,7-Tetrahydroimidazo[4,5-*c*]pyridine-5-carboxylic acid 2-(3-methylphenyl)ethyl ester oxalate

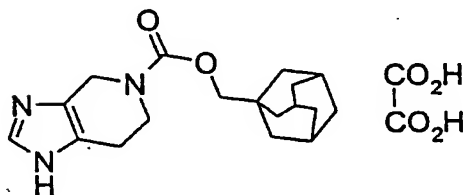


- 15 The compound was prepared from 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine and 2-(3-methylphenyl)-1-ethanol.

M.p. 155-157 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.27 (s, 3H), 2.52–2.65 (m, 2H), 2.85 (t, *J* = 5 Hz, 2H), 3.63 (s, br, 2H), 4.21 (t, *J* = 5 Hz, 2H), 4.40 (s, 2H), 7.02 (m, 3H), 7.18 (s, br, 1H), 8.16 (s, 1H).

(C₁₆H₁₉N₃O₂, C₂H₂O₄); calcd. 57.59C 5.64H 11.19N; found 57.33C 5.64H 11.13N.

Example 25: 4,5,6,7-Tetrahydro-imidazo[4,5-*c*]pyridine-5-carboxylic acid adamantan-1-ylmethyl ester oxalate

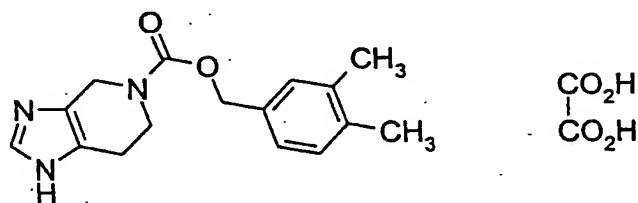


5

The compound was prepared from 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine and 1-adamantylmethanol.

10 M.p. 212-214 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.51 (s, 6H), 1.58–1.72 (m, 6H), 1.94 (s, br, 3H), 2.64 (s, br, 2H), 3.63–3.73 (m, 4H), 4.44 (m, 2H), 8.13 (s, br, 1H).

Example 26: 4,5,6,7-Tetrahydroimidazo[4,5-*c*]pyridine-5-carboxylic acid 3,4-dimethylbenzyl ester oxalate



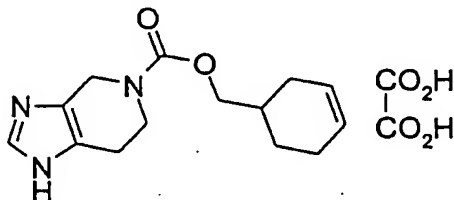
15

The compound was prepared from 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine and 3,4-dimethylbenzyl alcohol.

20 M.p. 193-195 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.20 (s, 6H), 2.62 (m, 2H), 3.69 (m, 2H), 4.45 (s, 2H), 5.03 (s, 2H), 7.05–7.14 (m, 3H), 8.12 (s, br, 1H).

Calcd. 57.59C 5.64H 11.19N; found 57.76C 5.60H 10.90N.

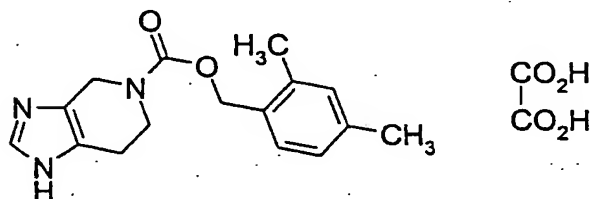
Example 27: 4,5,6,7-Tetrahydroimidazo[4,5-c]pyridine-5-carboxylic acid cyclohex-3-enylmethyl ester oxalate



The compound was prepared from 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine and cyclohexen-4-ylmethanol.

¹H NMR (400 MHz, DMSO-*d*₆) δ 1.26 (m, 1H), 1.70–1.80 (m, 2H), 1.82–1.92 (m, 1H), 1.98–2.10 (m, 3H), 2.63 (t, *J* = 5 Hz, 2H), 3.68 (t, *J* = 5 Hz, 2H), 3.94 (d, *J* = 7 Hz, 2H), 4.43 (s, br, 2H), 5.65 (m, 2H), 8.10 (s, br, 1H).

Example 28: 4,5,6,7-Tetrahydroimidazo[4,5-c]pyridine-5-carboxylic acid 2,4-dimethylbenzyl ester oxalate

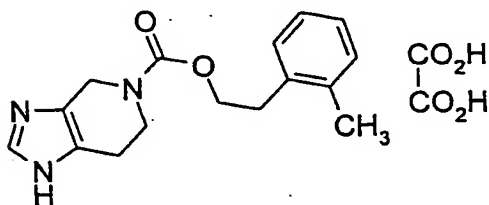


The compound was prepared from 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine and 2,4-dimethylbenzylalcohol.

M.p. 176-178 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.26 (s, 6H), 2.62 (m, 2H), 3.68 (m, 2H), 4.43 (s, 2H), 5.08 (s, 2H), 6.98 (d, *J* = 8 Hz, 1H), 7.02 (s, 1H), 7.19 (d, *J* = 8 Hz, 1H), 8.09 (s, br, 1H).

(C₁₆H₁₉N₃O₂, C₂H₂O₄); calcd. 57.59C 5.64H 11.19N; found 57.51C 5.63H 11.19N.

Example 29: 4,5,6,7-Tetrahydroimidazo[4,5-c]pyridine-5-carboxylic acid 2-(2-methylphenyl)ethyl ester oxalate

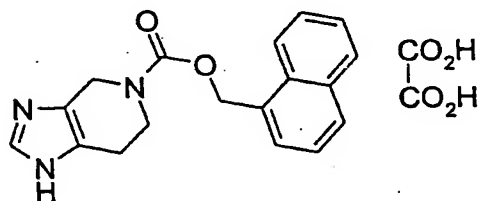


The compound was prepared from 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine and 2-(2-methylphenyl)ethanol.

10 ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 2.29 (s, 3H), 2.59 (s, br, 2H), 2.91 (m, 2H), 3.63 (s, br, 2H), 4.21 (t, $J = 5$ Hz, 2H), 4.41 (s, 2H), 7.06–7.20 (m, 4H), 8.15 (s, 1H).

($\text{C}_{16}\text{H}_{19}\text{N}_3\text{O}_2$, $\text{C}_2\text{H}_2\text{O}_4$); calcd. 57.59C 5.64H 11.19N; found 57.44C 5.63H 11.16N.

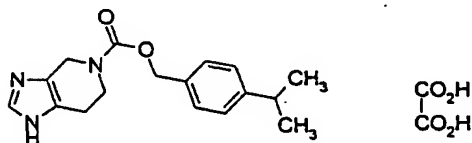
15 **Example 30:** 4,5,6,7-Tetrahydroimidazo[4,5-*c*]pyridine-5-carboxylic acid naphthalen-1-ylmethyl ester oxalate



The compound was prepared from 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine and 1-naphthylmethanol.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 2.52–2.68 (m, 2H), 3.69 (m, 2H), 4.43 (m, 2H), 5.58 (s, 2H), 7.46–7.62 (m, 4H), 7.92–8.00 (m, 2H), 8.05–8.15 (m, 2H).

Example 31: 4,5,6,7-Tetrahydroimidazo[4,5-c]pyridine-5-carboxylic acid 4-isopropylbenzyl ester oxalate



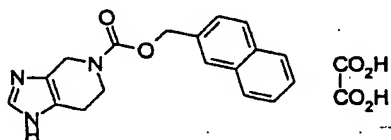
5

The compound was prepared from 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine and 4-isopropylbenzyl alcohol.

M.p. 166-168 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.19 (d, *J* = 7 Hz, 6H), 2.64 (m, 2H), 2.89 (sept, *J* = 7 Hz, 1H), 3.70 (t, *J* = 5 Hz, 2H), 4.46 (s, br, 2H), 5.07 (s, 2H), 7.23 (d, *J* = 8 Hz, 2H), 7.29 (d, *J* = 8 Hz, 2H), 8.18 (s, br, 1H).

(C₁₇H₂₃N₃O₂, C₂H₂O₄); calcd. 58.60C 5.95H 10.79N; found 58.71C 5.97H 10.76N.

Example 32: 4,5,6,7-Tetrahydroimidazo[4,5-*c*]pyridine-5-carboxylic acid naphthalen-2-ylmethyl ester oxalate



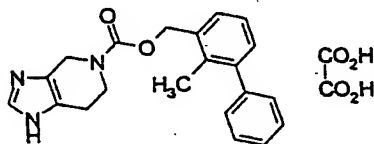
The compound was prepared from 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine and 2-naphthylmethanol.

M.p. 189-191 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.67 (m, 2H), 3.64 (m, 2H), 4.43-4.60 (m, 2H), 5.79 (s, 2H), 7.52-7.56 (m, 3H), 7.89-8.95 (m, 4H), 8.18 (s, br, 1H).

25

Calcd. 60.45C 4.82H 10.57N; found 60.33C 4.82H 10.53N.

Example 33: 4,5,6,7-Tetrahydroimidazo[4,5-c]pyridine-5-carboxylic acid 2-methylbiphenyl-3-ylmethyl ester oxalate



5

The compound was prepared from 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine and 2-methylbiphenyl-3-ylmethanol.

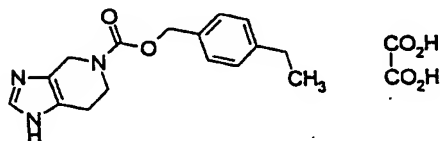
M.p. 151-153 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.18 (s, 3H), 2.68 (m, 2H), 3.71 (m, 2H), 4.48 (s, br, 2H), 5.19 (s, 2H), 7.18-7.48 (m, 8H), 8.16 (s, br, 1H).

10

(C₂₃H₂₃N₃O₆, 2/3 H₂O); calcd. 61.46C 5.46H 9.35N; found 61.62C 5.42H 8.94N.

15

Example 34: 4,5,6,7-Tetrahydroimidazo[4,5-*c*]pyridine-5-carboxylic acid 4-ethylbenzyl ester oxalate



20

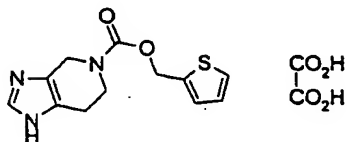
The compound was prepared from 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine and 4-ethylbenzyl alcohol.

M.p. 171-173 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.17 (t, *J* = 7 Hz, 3H), 2.55-2.68 (m, 4H), 3.69 (t, *J* = 5 Hz, 2H), 4.45 (s, br, 2H), 5.08 (s, 2H), 7.20 (d, *J* = 8 Hz, 2H), 7.29 (d, *J* = 8 Hz, 2H), 8.11 (s, br, 1H).

25

(C₁₆H₁₉N₃O₂, C₂H₂O₄); calcd. 57.59C 5.64H 11.19N; found 57.48C 5.61H 11.20N.

Example 35: 4,5,6,7-Tetrahydroimidazo[4,5-c]pyridine-5-carboxylic acid thiophen-2-ylmethyl ester oxalate



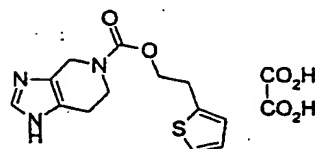
5

The compound was prepared from 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-c]pyridine and 2-thienylmethanol.

¹H NMR (400 MHz, DMSO-*d*₆) δ 2.63 (s, br, 2H), 3.68 (s, br, 2H), 4.43 (s, 2H), 5.28 (s, 2H), 7.01 (m, 1H), 7.17 (d, *J* = 3 Hz, 1H), 7.54 (d, *J* = 5 Hz, 1H), 8.10 (m, 1H).

10

Example 36: 4,5,6,7-Tetrahydroimidazo[4,5-c]pyridine-5-carboxylic acid 2-thiophen-2-ylethyl ester oxalate



15

The compound was prepared from 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-c]pyridine and 2-(2-thienyl)-1-ethanol.

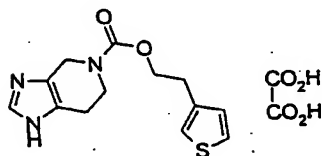
M.p. 173-175 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.62 (s, br, 2H), 3.13 (t, *J* = 7 Hz, 2H), 3.68 (t, *J* = 5 Hz, 2H), 4.21 (t, *J* = 7 Hz, 2H), 4.43 (s, br, 2H), 6.89–6.99 (m, 2H), 7.34 (s, br, 1H), 8.11 (s, br, 1H).

20

(C₁₃H₁₅N₃O₂S); calcd. 49.04C 4.66H 11.44N; found 49.12C 4.62H 11.43N.

25

Example 37: 4,5,6,7-Tetrahydroimidazo[4,5-c]pyridine-5-carboxylic acid 2-thiophen-3-ylethyl ester oxalate



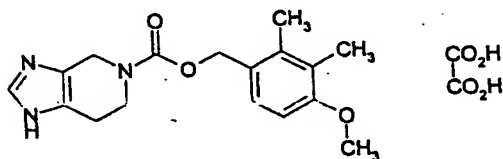
5

The compound was prepared from 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine and 2-(3-thienyl)-1-ethanol.

M.p. 193-194 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.59 (s, br, 2H), 2.93 (t, *J* = 7 Hz, 2H), 3.63 (s, br, 2H), 4.21 (t, *J* = 7 Hz, 2H), 4.40 (s, 2H), 7.03 (s, br, 1H), 7.24 (s, br, 1H), 7.46 (s, br, 1H), 8.08 (s, br, 1H).

(C₁₃H₁₅N₃O₂S); calcd. 49.04C 4.66H 11.44N; found 49.12C 4.61H 11.40N.

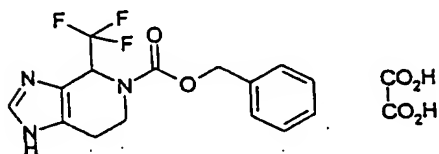
Example 38: 4,5,6,7-Tetrahydro-imidazo[4,5-*c*]pyridine-5-carboxylic acid 4-methoxy-2,3-dimethylbenzyl ester oxalate



The compound was prepared from 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine and 2,3-dimethyl-4-methoxybenzyl alcohol.

M.p. 161-162 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.09 (s, 3H), 2.20 (s, 3H), 2.62 (s, br, 2H), 3.65 (s, br, 2H), 3.77 (s, 3H), 4.42 (s, br, 2H), 5.08 (s, 2H), 6.78 (d, *J* = 8 Hz, 1H), 7.15 (d, *J* = 8 Hz, 1H), 8.18 (s, br, 1H).

Example 39: 4-Trifluoromethyl-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine-5-carboxylic acid benzyl ester oxalate



5

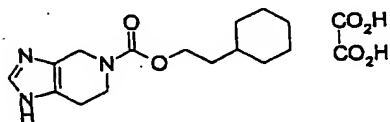
The compound was prepared from 4-trifluoromethyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine and benzyl alcohol.

M.p. 169-171 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.65–2.81 (m, 2H), 2.99 (s, br, 2H), 4.42 (q, *J* = 8 Hz, 1H), 5.42 (s, 2H), 7.36–7.45 (m, 3H), 7.51 (d, *J* = 8 Hz, 2H), 8.21 (s, 1H). 1H).

10

Example 40: 4,5,6,7-Tetrahydroimidazo[4,5-c]pyridine-5-carboxylic acid 2-cyclohexylethyl ester oxalate

15



The compound was prepared from 4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine and 2-cyclohexyl-1-ethanol.

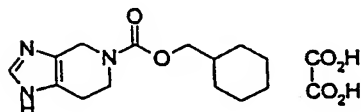
20

M.p. 174-176 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.83–0.95 (m, 2H), 1.05–1.26 (m, 3H), 1.32 (m, 1H), 1.48 (q, *J* = 7 Hz, 2H), 1.55–1.71 (m, 5H), 2.64 (m, 2H), 3.67 (t, *J* = 5 Hz, 2H), 4.06 (t, *J* = 7 Hz, 2H), 4.44 (s, 2H), 8.22 (s, br, 1H).

(C₁₅H₂₃N₃O₂); calcd. 55.58C 6.86H 11.40N; found 55.70C 6.90H 11.32N.

25

Example 41: 4,5,6,7-Tetrahydroimidazo[4,5-c]pyridine-5-carboxylic acid cyclohexylmethyl ester oxalate



5

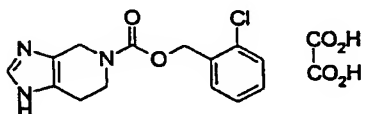
The compound was prepared from 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-c]pyridine and cyclohexylmethanol.

M.p. 176-178 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.89–1.03 (m, 2H), 1.06–1.29 (m, 3H), 1.55–1.72 (m, 6H), 2.65 (m, 2H), 3.68 (m, 2H), 3.86 (d, *J* = 7 Hz, 2H), 4.44 (s, br, 2H), 8.20 (s, br, 1H).

10

(C₁₄H₂₁N₃O₂, C₂H₂O₄) calcd. 54.38C 6.56H 11.89N; found 54.56C 6.64H 11.77N.

Example 42: 4,5,6,7-Tetrahydroimidazo[4,5-c]pyridine-5-carboxylic acid 2-chlorobenzyl ester oxalate



20

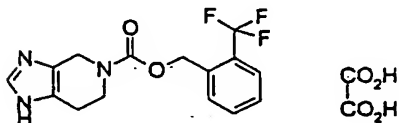
The compound was prepared from 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-c]pyridine and 2-chlorobenzyl alcohol.

M.p. 173-175 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.65 (m, 2H), 3.71 (s, br, 2H), 4.48 (m, 2H), 5.19 (s, 2H), 7.38 (m, 2H), 7.50 (m, 2H), 8.09 (s, br, 1H).

25

(C₁₄H₁₄ClN₃O₂, C₂H₂O₄); calcd. 50.34C 4.22H 11.01N; found 50.21C 4.19H 10.81N.

Example 43: 4,5,6,7-Tetrahydroimidazo[4,5-c]pyridine-5-carboxylic acid 2-trifluoromethylbenzyl ester oxalate



5

The compound was prepared from 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine and 2-(trifluoromethyl)benzyl alcohol.

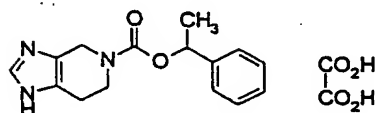
M.p. 152-156 °C (EtOAc). ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.67 (m, 2H), 3.71 (m, 2H), 4.48 (s, br, 2H), 5.28 (s, 2H), 7.58 (t, *J* = 8 Hz, 1H), 7.65–7.81 (m, 3H), 8.14 (m, 1H).

10

(C₁₅H₁₄F₃O₂, C₂H₂O₄); calcd. 49.16C 3.88H 10.12N; found 49.21C 3.86H 10.11N.

Example 44: 4,5,6,7-Tetrahydroimidazo[4,5-*c*]pyridine-5-carboxylic acid 1-phenylethyl ester oxalate

15



The compound was prepared from 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine and 1-phenylethanol.

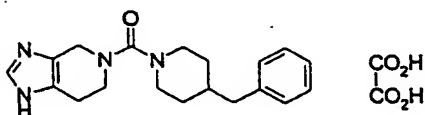
20

M.p. 162 °C (decomposes; EtOAc/MeOH). ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.49 (d, *J* = 7 Hz, 3H), 2.62 (s, br, 2H), 3.62–3.80 (m, 2H), 4.38–4.60 (m, 2H), 5.74 (q, *J* = 7 Hz, 1H), 7.25–7.40 (m, 5H), 8.06 (s, br, 1H).

25

Calcd. 56.51C 5.30H 11.63N; found 56.46C 5.28H 11.48N.

Example 45: (4-Benzylpiperidin-1-yl)-(4,5,6,7-tetrahydroimidazo[4,5-c]pyridin-5-yl)-methanone oxalate



5

The compound was prepared from 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine and 4-benzylpiperidine according to the following, general procedure for the preparation of uréas:

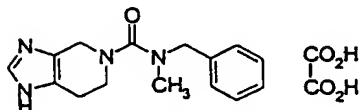
- 10 A solution of 4-nitrophenyl chloroformate (1.04 g, 5.2 mmol) in DCM (10 mL) was dropwise added to a solution of 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine (1.0 g, 4.7 mmol) in methanol (14 mL) and triethylamine (1.9 mL). The resulting mixture was stirred at 20 °C for 1 h, concentrated under reduced pressure, and the residue was distributed between DCM (40 mL) and water (40 mL). After separation of phases the
- 15 aqueous phase was extracted with DCM (1 x 40 mL), and the combined organic phases were dried (MgSO₄) and concentrated. The residue was dissolved in DMF (20 mL), 4-benzylpiperidine (1.65 mL, 9.39 mmol) was added, and the resulting mixture was stirred at 80 °C for 17 h. The mixture was concentrated under reduced pressure, and the residue was redissolved in ethyl acetate. After washing with water
- 20 the organic phase was dried (MgSO₄) and filtered. To the filtrate was added a solution of oxalic acid (0.44 g, 4.9 mmol) in ethyl acetate, and the resulting precipitate is filtered off. The resulting solid was distributed between an aqueous solution of NaHCO₃ and ethyl acetate, and the organic layer was purified by column chromatography. The purified compound was again precipitated as oxalate from ethyl acetate to
- 25 yield 0.58 g (30%) of the title oxalate as colorless solid, which does not melt but decomposes upon heating.

¹H NMR (400 MHz, DMSO-*d*₆) δ 1.06–1.20 (m, 2H), 1.52–1.60 (m, 2H), 1.61–1.75 (m, 1H), 2.52 (m, 2H), 2.65–2.78 (m, 4H), 3.42 (t, *J* = 5 Hz, 2H), 3.55–3.63 (m, 2H),

30 4.23 (s, 2H), 7.16–7.31 (m, 5H), 8.40 (s, 1H).

Anal. calcd. for $C_{19}H_{24}N_4O$, 1.5 $C_2H_2O_4$ (459.49): 57.51C 5.92H 12.19N; found: 57.67C 6.20H 12.25N.

Example 46: 4,5,6,7-Tetrahydroimidazo[4,5-c]pyridine-5-carboxylic acid *N*-methyl-*N*-benzylamide oxalate

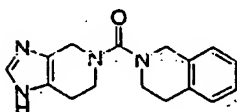


The compound was prepared in the same way as disclosed for example 45 from 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine and benzylmethylamine.

M.p. 164-166 °C (EtOAc/MeOH). 1H NMR (400 MHz, DMSO- d_6) δ 2.71 (m, 5H), 3.49 (t, J = 5 Hz, 2H), 4.23 (s, 2H), 4.36 (s, 2H), 7.23–7.39 (m, 5H), 8.19 (s, 1H).

Calcd. 56.66C 5.59H 15.55N; found 56.75C 5.61H 15.35N.

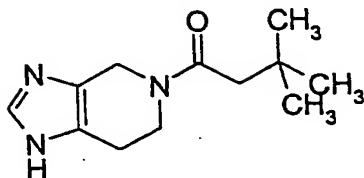
Example 47: (3,4-Dihydro-1*H*-isoquinolin-2-yl)(4,5,6,7-tetrahydroimidazo[4,5-*c*]pyridin-5-yl)methanone



The compound was prepared in the same way as disclosed for example 45 from 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine and benzylmethylamine.

M.p. 102-104 °C (EtOAc). 1H NMR (400 MHz, DMSO- d_6) δ 2.66 (s, br, 2H), 2.84 (t, J = 5 Hz, 2H), 3.46 (m, 4H), 4.21 (s, br, 2H), 4.39 (s, 2H), 7.16 (s, 4H), 7.47 (s, 1H), 11.80 (s, 1H).

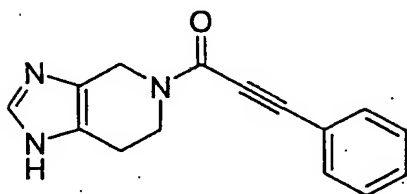
Example 48: 3,3-Dimethyl-1-(1,4,6,7-tetrahydroimidazo[4,5-c]pyridin-5-yl)-butan-1-one



5 At 0 °C, EDC (0.45 g, 2.4 mmol) was added to a solution of tert-butylacetic acid (0.30 mL, 2.3 mmol), and 1-hydroxy-7-azabenzotriazole (0.32 g, 2.4 mmol) in dichloromethane (30 mL). The reaction mixture was stirred for 20 min at 0 °C. 4,5,6,7-tetrahydroimidazo[4,5-c]pyridine dihydrochloride (0.50 g, 2.4 mmol) was added. Ethyldi-
10 isopropylamine (0.40 mL, 2.4 mmol) was added. The reaction mixture was stirred for 16 h at room temperature. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with 10% aqueous sodium hydrogen sulfate solution (100 mL). A 1 N solution of sodium hydroxide was added to the aqueous solution until pH 12 was obtained. It was extracted with ethyl acetate (2 x 100 mL). These organic extracts
15 were dried over magnesium sulfate. The solvent was removed *in vacuo*. The crude product was purified by flash chromatography on silica (40 g), using dichloromethane/methanol/25% aqueous ammonia (100:10:1) as eluent to give 125 mg of the title compound.

20 ¹H NMR (CDCl₃, 2 rotamers): δ 1.03 and 1.10 (both s, together 9 H); 2.35 and 2.40 (both s, together 2 H); 2.68 and 2.78 (both t, together 2 H); 3.80 and 3.95 (both t, together 2 H); 4.55 and 4.70 (both s, together 2 H); 7.53 (s, 1 H).

For biological testing it was transferred into its acetate salt by lyophilization with
25 0.5 M acetic acid (40 mL).

Example 49: 3-Phenyl-1-(1,4,6,7-tetrahydroimidazo[4,5-c]pyridin-5-yl)propynone

5 1-Hydroxy-7-azabenzotriazole (0.32 g, 2.4 mmol) was added to a solution of phenyl-propionic acid (0.34 g, 2.4 mmol) in dichloromethane (30 mL). The solution was cooled to 0 °C. EDC (0.45 g, 2.4 mmol) was added. The reaction mixture was stirred at 0 °C for 20 min. 4,5,6,7-Tetrahydroimidazo[4,5-c]pyridine dihydrochloride (0.50 g, 2.3 mmol) was added. Ethyldiisopropylamine (0.40 mL, 2.3 mmol) was added. The
10 reaction mixture was stirred for 16 h at room temperature. It was diluted with ethyl acetate (100 mL) and washed with 10% aqueous sodium hydrogensulfate solution (100 mL). The aqueous phase was extracted with ethyl acetate (3 x 60 mL). It was added a 1 N sodium hydroxide solution until pH 12 was obtained. It was extracted with ethyl acetate (3 x 90 mL). These extracts were combined and dried over magne-
15 sium sulfate. The solvent was removed *in vacuo*. The crude product was purified by flash chromatography on silica (40 g), using dichloromethane/methanol/25% aqueous ammonia (100:10:1) as eluent, to give 50 mg of the title compound.

¹H NMR (CDCl₃, 2 rotamers): δ 2.75 and 2.85 (both t, together 2 H); 4.03 and 4.15
20 (both t, together 2 H); 4.75 and 4.92 (both s, together 1 H); 7.10 - 7.70 (m, 6 H).

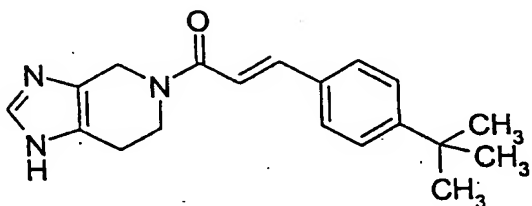
The title compound was transferred into its oxalate salt by dissolving in ethyl acetate (20 mL) and addition of a solution of oxalic acid in ethyl acetate (20 mL). The precipitation was collected and washed with ethyl acetate (10 mL). It was dried *in vacuo*.

25

HPLC : R_t = 6.922 min (Method h8).

LC-MS calcd. for MH⁺: 252 found: 252.

Example 50: 2E-3-(4-*tert*-Butylphenyl)-1-(1,4,6,7-tetrahydroimidazo[4,5-*c*]pyridin-5-yl)propenone



5

At 0 °C, EDC (0.45 g, 2.4 mmol) was added to a solution of 3-(4-*tert*-butylphenyl)-acrylic acid (0.48 g, 2.4 mmol) and 1-hydroxy-7-azabenzotriazole (0.32 g, 2.4 mmol) in dichloromethane (30 mL). The reaction mixture was stirred for 20 min at 0 °C. 4,5,6,7-Tetrahydroimidazo[4,5-*c*]pyridine dihydrochloride (0.50 g, 2.3 mmol) was added. Ethyldiisopropylamine (0.40 mL, 2.3 mmol) was added. The reaction mixture was stirred for 16 h at room temperature. It was diluted with ethyl acetate (100 mL) and washed with a saturated aqueous solution of sodium hydrogencarbonate (100 mL). The aqueous phase was extracted with ethyl acetate (2 x 60 mL). The combined organic layers were dried over magnesium sulfate. The solvent was removed *in vacuo*. The crude product was purified by flash chromatography on silica (40 g), using dichloromethane/methanol/25% aqueous ammonia (100:10:1) as eluent, to give 119 mg of the title compound.

15

¹H NMR (CDCl₃): δ 1.32 (s, 9 H); 2.75 (br, 2 H); 3.95 (br, 2 H); 4.75 (br, 2 H); 6.95 (d, 1 H); 7.35 - 7.55 (m, 5 H); 7.65 (d, 1 H).

20

For biological testing, the title compound was transferred into its oxalate salt: The title compound was dissolved in ethyl acetate (15 mL). A solution of oxalic acid (58 mg, 0.64 mmol) in ethyl acetate (15 mL) was added. The precipitation was collected, washed with ethyl acetate (10 mL) and dried *in vacuo*.

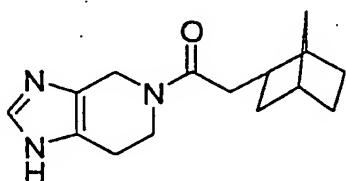
25

HPLC: R_t 9.55 min (Method h8).

LC-MS: calcd. for MH^+ : 310; found 310.

Example 51: 2-Bicyclo[2.2.1]hept-2-yl-1-(1,4,6,7-tetrahydroimidazo[4,5-c]pyridin-5-yl)ethanone

5



At 0 °C, EDC (0.45 g, 2.4 mmol) was added to a solution of 1-hydroxy-7-azabenzotriazole (0.32 g, 2.4 mmol) and 2-norbornaneacetic acid (0.338 mL, 2.4 mmol) in dichloromethane (30 mL). The reaction mixture was stirred for 20 min at 0 °C. 4,5,6,7-Tetrahydroimidazo[4,5-c]pyridine dihydrochloride (0.50 g, 2.3 mmol) was added. Ethyldiisopropylamine (0.40 mL, 2.3 mmol) was added. The reaction mixture was stirred for 16 h at room temperature. It was diluted with ethyl acetate (100 mL) and washed with a saturated aqueous solution of sodium hydrogencarbonate (100 mL). The aqueous solution was extracted with ethyl acetate (2 x 60 mL). The combined organic layers were dried over magnesium sulfate. The solvent was removed *in vacuo*. The crude product was purified by flash chromatography on silica (40 g), using dichloromethane/methanol/25% aqueous ammonia (100:10:1) as eluent, to give 120 mg of the title compound.

20

1H NMR ($CDCl_3$, 2 rotamers): δ 1.00 - 2.50 (m, 13 H); 2.65 and 2.75 (both t, together 2 H); 3.75 and 3.90 (both t, together 2 H); 4.55 and 4.65 (both s, together 2 H); 7.53 (s, 1 H).

For biological testing, the title compound was transferred into its oxalate salt: The title compound was dissolved in ethyl acetate (15 mL). A solution of oxalic acid (42 mg, 0.47 mmol) in ethyl acetate (15 mL) was added. The precipitation was collected, washed with ethyl acetate (10 mL) and dried *in vacuo*.

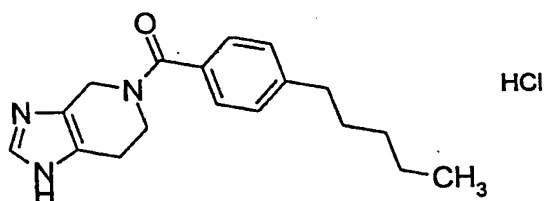
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HPLC: R_t = 7.59 min (Method h8).

LC-MS: calcd. for MH^+ : 260; found 260.

- 5 $C_{15}H_{21}N_3O \cdot C_2H_2O_4$ (349.39)
calcd: 58.44C 6.64H 12.03N;
found: 58.72C 6.70H 11.99N.

10 **Example 52: 4-Pentylphenyl-(1,4,6,7-tetrahydroimidazo[4,5-c]pyridin-5-yl)methanone hydrochloride**



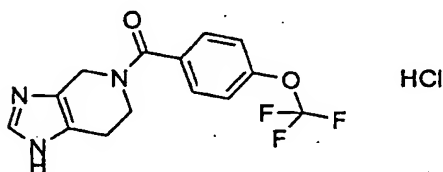
- 15 To a solution of 4-pentylbenzoic acid (0.77 g, 4 mmol) in DMF (10 mL) was added carbonyl diimidazole (0.65 g, 4 mmol) and the mixture was stirred at room temperature for 2 h. 4,5,6,7-Tetrahydro-1H-imidazo[4,5-c]pyridine (0.81 g, 3.8 mmol) and triethylamine (1.6 mL) were added and the mixture was stirred at room temperature overnight.
- 20 The mixture was concentrated under reduced pressure, and water (50 mL) and ethyl acetate (50 mL) were added to the residue. The organic phase was washed with water twice, with brine, dried ($MgSO_4$), and mixed with a solution of oxalic acid (0.35 g) in ethyl acetate (20 mL). The mixture was kept at room temperature overnight, filtered, and the resulting solid was dried under reduced pressure. 1.08 g (73%) of the
- 25 colourless oxalate were obtained.

The oxalate was dissolved in water (50 mL) and sodium hydroxide (2 mL, 4N in water) was added. The free base was extracted with ethyl acetate (2 x 100 mL), and after drying ($MgSO_4$) and concentration it was redissolved in hydrochloric acid (1N in

water). Concentration and precipitation from acetone yielded 0.45 g (36%) of the title compound as colourless solid.

M.p. 180-183 °C. ¹H NMR (300 MHz, DMSO-*d*₆): δ 0.88 (t, *J* = 7 Hz, 3H), 1.22-1.40 (m, 4H), 1.59 (quintt, *J* = 7 Hz, 2H), 2.62 (t, *J* = 7 Hz, 2H), 2.78 (m, 2H), 3.1-4.1 (m, 4H), 7.30 (d, *J* = 8 Hz, 2H), 7.39 (d, *J* = 8 Hz, 2H), 8.95 (s, 1H), 14.65 (s, br, 1H).

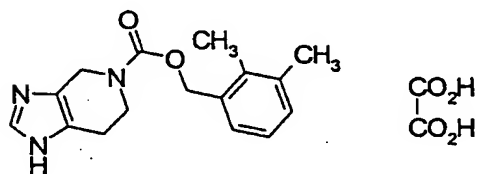
Example 53: 4-Trifluoromethoxyphenyl-(1,4,6,7-tetrahydroimidazo[4,5-*c*]pyridin-5-yl)-methanone hydrochloride



The compound was prepared in the same way as example 52 from 4-trifluoromethoxybenzoic acid and 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine.

M.p. 239-242 °C. ¹H NMR (300 MHz, DMSO-*d*₆): δ 2.80 (m, 2H), 3.0-4.8 (m, 4H), 7.48 (d, *J* = 8 Hz, 2H), 7.65 (d, *J* = 8 Hz, 2H), 8.98 (s, 1H), 14.75 (s, br, 1H).

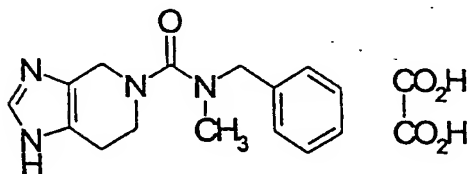
Example 54: 4-Trifluoromethylphenyl-(1,4,6,7-tetrahydroimidazo[4,5-*c*]pyridin-5-yl)methanone oxalate



The compound was prepared in the same way as example 52 from 4-trifluoromethylbenzoic acid and 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine.

M.p. 201-203 °C. ¹H NMR (mixture of rotamers, 400 MHz, DMSO-*d*₆): δ 2.66-2.80 (m, 2H), 3.54 (s, br, 1.5H), 3.96 (s, br, 0.5H), 4.38 (s, br, 0.5H), 4.69 (s, 1.5H), 7.68 (m, 2H), 7.85 (d, *J* = 8 Hz, 2H), 8.02 (s, br, 0.25H), 8.20 (s, 0.75H).

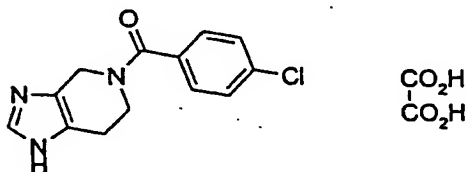
Example 55: 4-Isobutylphenyl-(1,4,6,7-tetrahydroimidazo[4,5-*c*]pyridin-5-yl)methanone oxalate



The compound was prepared in the same way as example 52 from 4-isobutylbenzoic acid and 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine.

M.p. 185-186 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.88 (d, *J* = 7 Hz, 6H), 1.88 (sept, *J* = 7 Hz, 1H), 2.50 (d, *J* = 7 Hz, 2H), 2.71 (s, br, 2H), 3.55-3.99 (m, 2H), 4.38-4.65 (m, 2H), 7.25 (d, *J* = 8 Hz, 2H), 7.38 (d, *J* = 8 Hz, 2H), 7.98-8.21 (m, 1H).

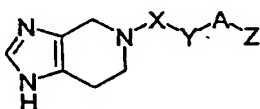
Example 56: 4-Chlorophenyl-(1,4,6,7-tetrahydroimidazo[4,5-*c*]pyridin-5-yl)methanone oxalate



The compound was prepared in the same way as example 52 from 4-chlorobenzoic acid and 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine.

M.p. 228-230 °C. ^1H NMR (mixture of rotamers, 400 MHz, DMSO- d_6): δ 2.72 (s, br, 2H), 3.56 (s, br, 1.5H), 3.93 (s, br, 0.5H), 4.42 (s, br, 0.5H), 4.64 (s, 1.5H), 7.48 (d, J = 8 Hz, 2H), 7.53 (d, J = 8 Hz, 2H), 8.02 (s, br, 0.25H), 8.18 (s, 0.75H).

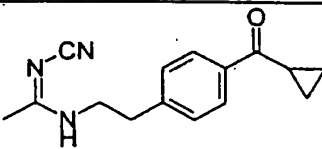
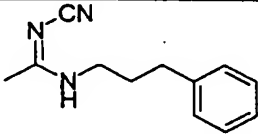
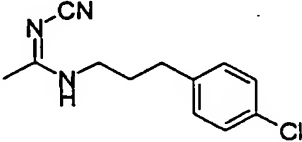
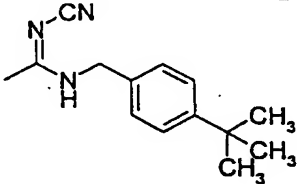
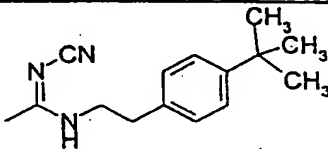
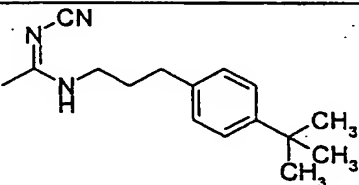
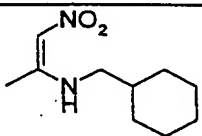
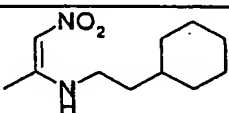
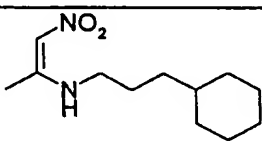
Furthermore, the following preferred compounds according to the invention may be prepared according to the general procedures set forth in the foregoing description:

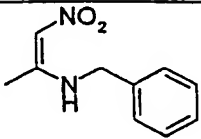
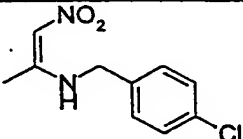
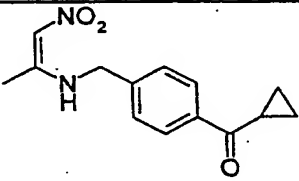
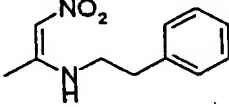
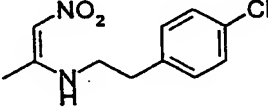
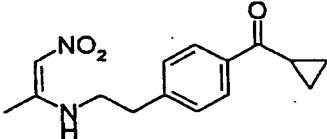
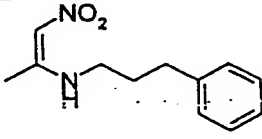
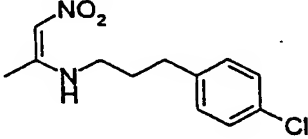
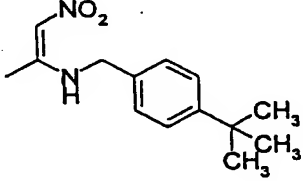


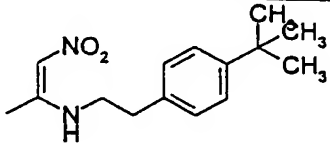
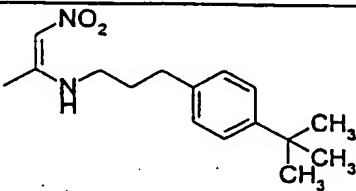
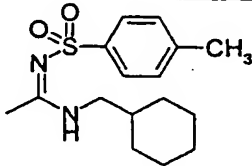
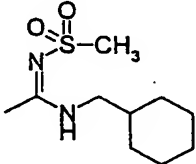
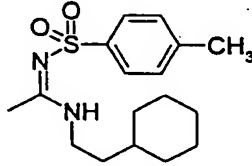
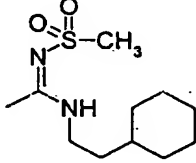
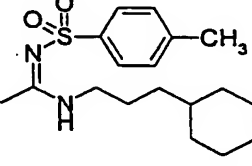
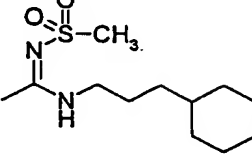
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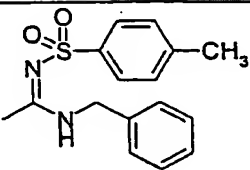
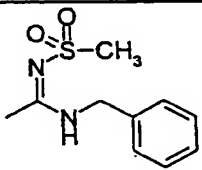
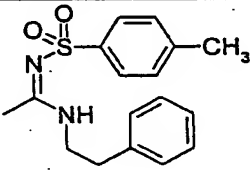
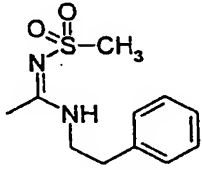
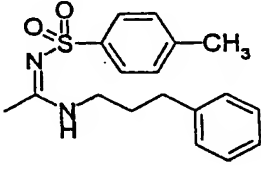
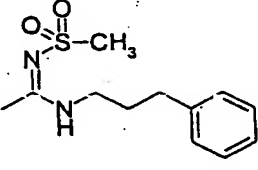
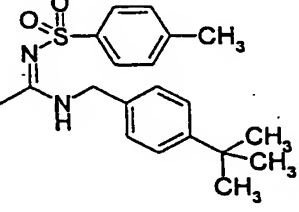
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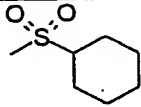
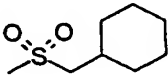
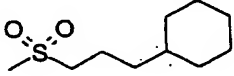
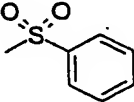
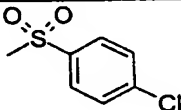
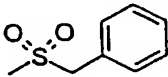
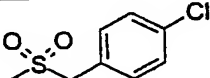
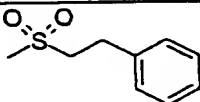
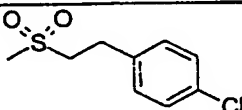
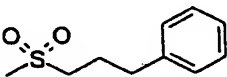
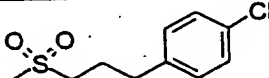
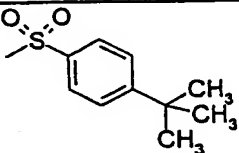
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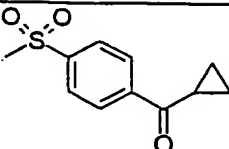
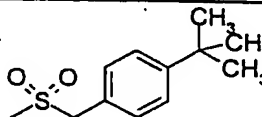
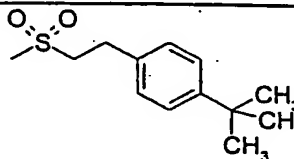
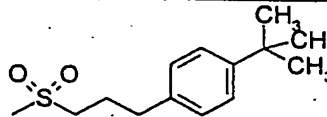
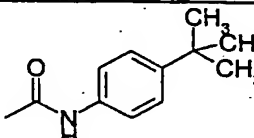
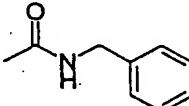
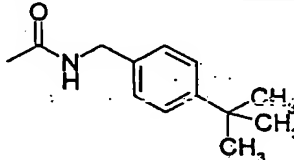
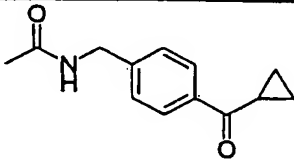
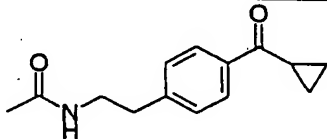
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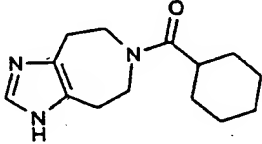
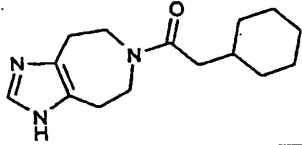
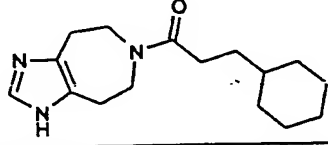
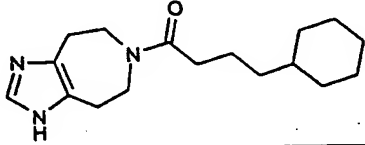
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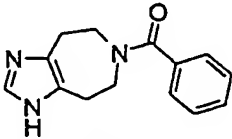
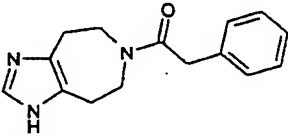
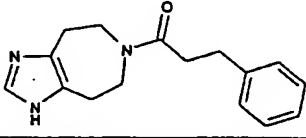
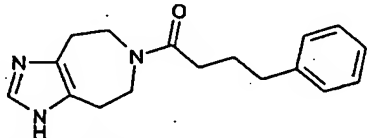
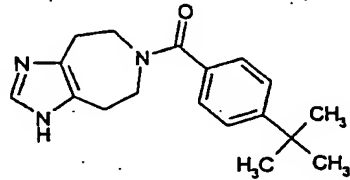
97	 <chem>CC(=N1S(=O)(=O)C1)NCc2ccc(C(C)(C)C)cc2</chem>
98	 <chem>CC(=N1S(=O)(=O)C1)NCc2ccc(C3CC3C(=O)c4ccccc4)cc2</chem>
99	 <chem>CC(=N1S(=O)(=O)C1)NCc2ccc(C3CC3C(=O)c4ccccc4)cc2</chem>
100	 <chem>CC(=N1S(=O)(=O)C1)NCc2ccc(C(C)(C)C)cc2</chem>
101	 <chem>CC(=N1S(=O)(=O)C1)NCc2ccc(C(C)(C)C)cc2</chem>
102	 <chem>CC(=N1S(=O)(=O)C1)NCc2ccc(C(C)(C)C)cc2</chem>
103	 <chem>CC(=N1S(=O)(=O)C1)NCc2ccc(C(C)(C)C)cc2</chem>

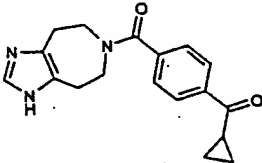
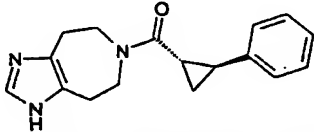
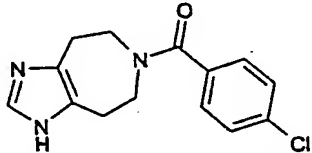
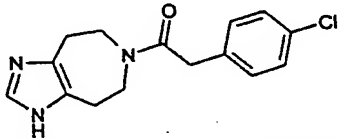
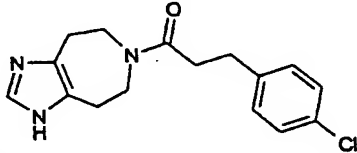
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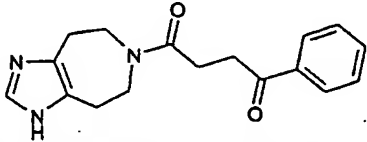
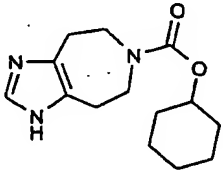
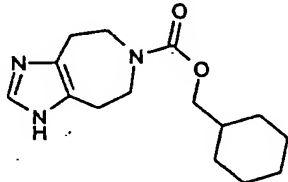
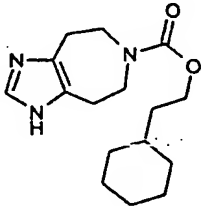
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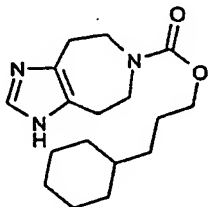
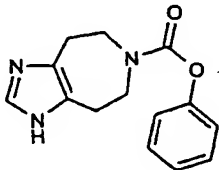
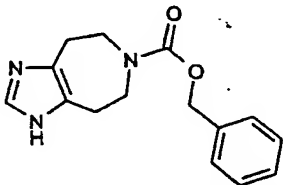
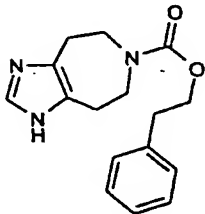
The following examples were prepared according to General Procedure C, D or E.
The molecular weights of the examples were all confirmed by MS:

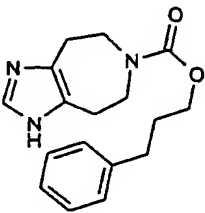
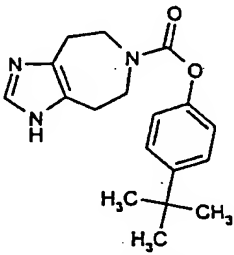
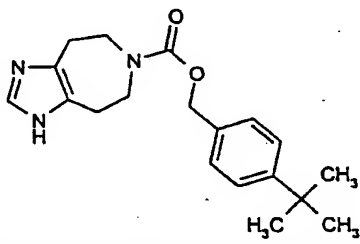
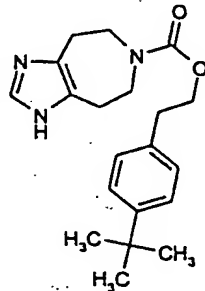
Example No	Name/Structure	Purity (%) (HPLC/UV)	MW
125	Cyclohexyl-(4,5,7,8-tetrahydroimidazo[4,5-d]azepin-6-yl)methanone 	90	247.3
126	Cyclohexylmethyl-(4,5,7,8-tetrahydroimidazo[4,5-d]azepin-6-yl)methanone 	90	261.4
127	(2-Cyclohexylethyl)-(4,5,7,8-tetrahydroimidazo[4,5-d]azepin-6-yl)methanone 	90	275.4
128	(3-Cyclohexylpropyl)-(4,5,7,8-tetrahydroimidazo[4,5-d]azepin-6-yl)methanone 	90	289.4

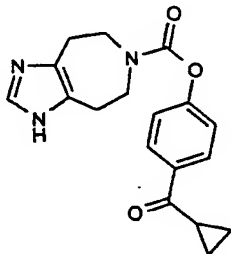
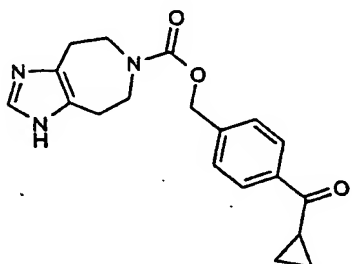
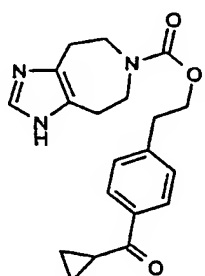
129	Phenyl-(4,5,7,8-tetrahydroimidazo[4,5-d]azepin-6-yl)methanone 	92	241.3
130	Benzyl-(4,5,7,8-tetrahydroimidazo[4,5-d]azepin-6-yl)methanone 	90	255.3
131	(2-Phenylethyl)-(4,5,7,8-tetrahydroimidazo[4,5-d]azepin-6-yl)methanone 	90	269.3
132	(3-Phenylpropyl)-(4,5,7,8-tetrahydroimidazo[4,5-d]azepin-6-yl)methanone 	92	283.4
133	(4-tert-Butylphenyl)-(4,5,7,8-tetrahydroimidazo[4,5-d]azepin-6-yl)methanone 	92	297.4

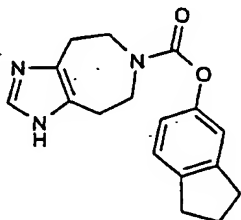
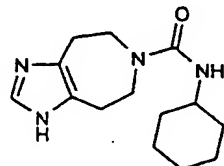
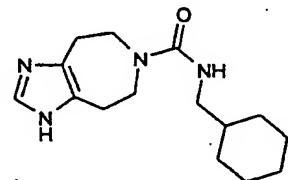
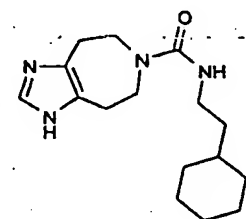
134	(4-Cyclopropanoylphenyl)-(4,5,7,8-tetrahydroimidazo[4,5- <i>d</i>]azepin-6-yl)methanone	90	309.4
			
135	(<i>trans</i> -2-Phenylcyclopropyl)-(4,5,7,8-tetrahydroimidazo[4,5- <i>d</i>]azepin-6-yl)methanone	90	281.4
			
136	4-Chlorophenyl-(4,5,7,8-tetrahydroimidazo[4,5- <i>d</i>]azepin-6-yl)methanone	83	275.7
			
137	(4-Chlorophenylmethyl)-(4,5,7,8-tetrahydroimidazo[4,5- <i>d</i>]azepin-6-yl)methanone	90	289.8
			
138	(2-(4-Chlorophenyl)ethyl)-(4,5,7,8-tetrahydroimidazo[4,5- <i>d</i>]azepin-6-yl)methanone	90	303.8
			

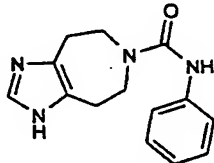
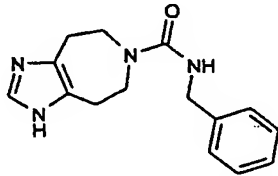
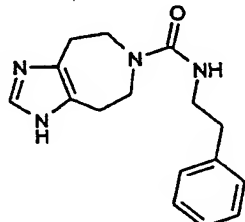
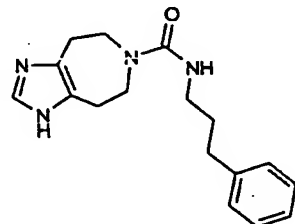
139	(2-Benzoyl-ethyl)-(4,5,7,8-tetrahydroimidazo[4,5-d]azepin-6-yl)methanone 	92	297.4
140	4,5,7,8-Tetrahydroimidazo[4,5-d]azepine-6-carboxylic acid cyclohexyl ester 	97	263.3
141	4,5,7,8-Tetrahydroimidazo[4,5-d]azepine-6-carboxylic acid cyclohexylmethyl ester 	92	277.4
142	4,5,7,8-Tetrahydroimidazo[4,5-d]azepine-6-carboxylic acid (2-cyclohexylethyl) ester 	82	291.4

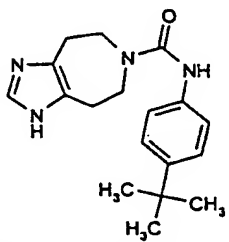
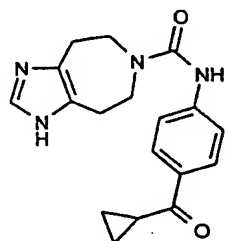
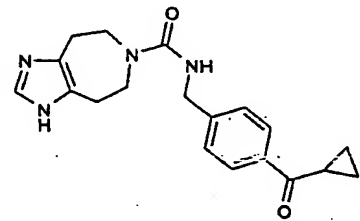
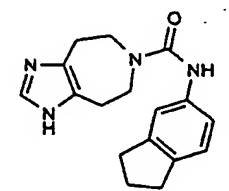
143	4,5,7,8-Tetrahydroimidazo[4,5-d]azepine-6-carboxylic acid (3-cyclohexylpropyl) ester 	75	305.4
144	4,5,7,8-Tetrahydroimidazo[4,5-d]azepine-6-carboxylic acid phenyl ester 	75	257.3
145	4,5,7,8-Tetrahydroimidazo[4,5-d]azepine-6-carboxylic acid benzyl ester 	95	271.3
146	4,5,7,8-Tetrahydroimidazo[4,5-d]azepine-6-carboxylic acid (2-phenylethyl) ester 	97	285.3

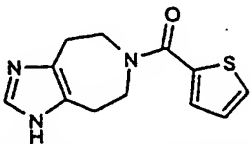
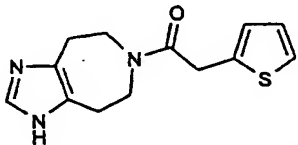
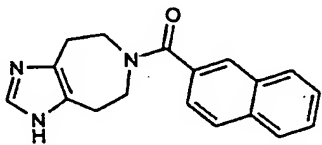
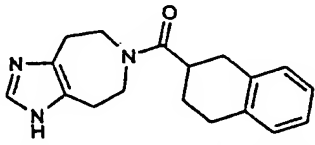
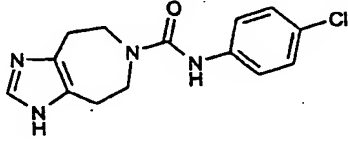
147	4,5,7,8-Tetrahydroimidazo[4,5-d]azepine-6-carboxylic acid 3-phenylpropyl ester	94	299.4
			
148	4,5,7,8-Tetrahydroimidazo[4,5-d]azepine-6-carboxylic acid 4- <i>tert</i> -butylphenyl ester	92	313.4
			
149	4,5,7,8-Tetrahydroimidazo[4,5-d]azepine-6-carboxylic acid 4- <i>tert</i> -butylphenylmethyl ester	91	327.4
			
150	4,5,7,8-Tetrahydroimidazo[4,5-d]azepine-6-carboxylic acid 4- <i>tert</i> -butylphenylethyl ester	95	341.5
			

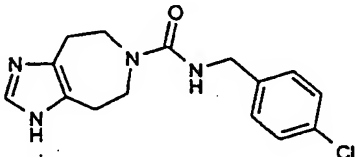
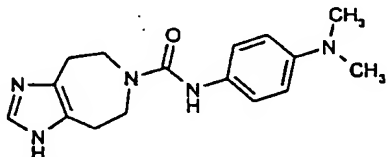
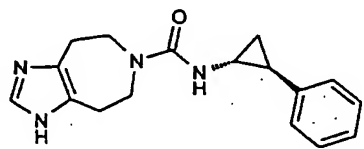
151	4,5,7,8-Tetrahydroimidazo[4,5-d]azepine-6-carboxylic acid 4-cyclopropanoylphenyl ester 	90	325.4
152	4,5,7,8-Tetrahydroimidazo[4,5-d]azepine-6-carboxylic acid 4-cyclopropanoylphenylmethyl ester 	95	339.4
153	4,5,7,8-Tetrahydroimidazo[4,5-d]azepine-6-carboxylic acid 2-(4-cyclopropanoylphenyl)ethyl ester 	95	353.4

154	4,5,7,8-Tetrahydroimidazo[4,5-d]azepine-6-carboxylic acid indan-5-yl ester	86	297.4
			
155	4,5,7,8-Tetrahydroimidazo[4,5-d]azepine-6-carboxylic acid cyclohexyl amide	90	262.4
			
156	4,5,7,8-Tetrahydroimidazo[4,5-d]azepine-6-carboxylic acid cyclohexylmethyl amide	90	276.4
			
157	4,5,7,8-Tetrahydroimidazo[4,5-d]azepine-6-carboxylic acid 2-cyclohexylethyl amide	92	290.4
			

158	4,5,7,8-Tetrahydroimidazo[4,5-d]azepine-6-carboxylic acid anilide 	99	256.3
159	4,5,7,8-Tetrahydroimidazo[4,5-d]azepine-6-carboxylic acid benzylamide 	90	270.3
160	4,5,7,8-Tetrahydroimidazo[4,5-d]azepine-6-carboxylic acid 2-phenylethylamide 	90	284.4
161	4,5,7,8-Tetrahydroimidazo[4,5-d]azepine-6-carboxylic acid 3-phenylpropylamide 	90	298.4

162	4,5,7,8-Tetrahydroimidazo[4,5-d]azepine-6-carboxylic acid 4- <i>tert</i> -butylphenyl amide 	98	312.4
163	4,5,7,8-Tetrahydroimidazo[4,5-d]azepine-6-carboxylic acid 4-cyclopropanoylphenyl amide 	90	324.4
164	4,5,7,8-Tetrahydroimidazo[4,5-d]azepine-6-carboxylic acid (4-cyclopropanoylphenyl)methyl amide 	90	338.4
165	4,5,7,8-Tetrahydroimidazo[4,5-d]azepine-6-carboxylic acid indan-5-yl amide 	98	296.4

166	2-Thienyl(4,5,7,8-tetrahydroimidazo[4,5-d]azepin-6-yl)methanone 	90	247.3
167	(2-Thienylmethyl)(4,5,7,8-tetrahydroimidazo[4,5-d]azepin-6-yl)methanone 	90	261.3
168	2-Naphthyl(4,5,7,8-tetrahydroimidazo[4,5-d]azepin-6-yl)methanone 	90	291.4
169	(1,2,3,4-Tetrahydronaphthalen-2-yl)(4,5,7,8-tetrahydroimidazo[4,5-d]azepin-6-yl)methanone 	90	295.4
170	4,5,7,8-Tetrahydroimidazo[4,5-d]azepine-6-carboxylic acid 4-chlorophenyl amide 	91	290.8

171	4,5,7,8-Tetrahydroimidazo[4,5- <i>d</i>]azepine-6-carboxylic acid 4-chlorobenzyl amide 	97	304.8
172	4,5,7,8-Tetrahydroimidazo[4,5- <i>d</i>]azepine-6-carboxylic acid 4-dimethylaminophenyl amide 	76	299.4
173	4,5,7,8-Tetrahydroimidazo[4,5- <i>d</i>]azepine-6-carboxylic acid trans-2-phenylcyclopropyl amide 	98	296.4

PHARMACOLOGICAL METHODS

The ability of the compounds to interact with the histamine H₃ receptor was determined by the following *in vitro* binding assays.

Binding assay I

Rat cerebral cortex was homogenized in ice cold K-Hepes, 5 mM MgCl₂ pH 7.1 buffer. After two differential centrifugations the last pellet was resuspended in fresh Hepes buffer containing 1 mg/mL bacitracin. Aliquots of the membrane suspension (400 mg/mL) were incubated for 60 min at 25°C with 30 pM [¹²⁵I]-iodoproxifan, a known histamine H₃ receptor antagonist, and the test compound at various concentrations. The incubation was stopped by dilution with ice-cold medium, followed by rapid filtration through Whatman GF/B filters pretreated for 1 h with 0.5% polyethylenimine. The radioactivity retained on the filters was counted using a Cobra II auto gamma counter. The radioactivity of the filters was indirectly proportional to the bind-

ing affinity of the tested compound. The results were analyzed by nonlinear regression analysis.

Binding assay II

- 5 The H₃-receptor agonist ligand R- α -methyl[³H]histamine was incubated with isolated rat cortex cell-membranes at 25 °C for 1h, followed by a filtration of the incubate through Whatman GF/B filters. Radioactivity retained on the filters was measured using a beta counter.
- 10 Male Wistar rats (150-200 g) were decapitated and cerebral cortex was quickly dissected out and frozen immediately on dry ice. Tissue was kept at -80 °C until membrane preparation. During the membrane preparation the tissue was kept on ice all the time. Rat cerebral cortex was homogenized in 10 volumes (w/w) ice-cold Hepes buffer (20 mM Hepes, 5 mM MgCl₂ pH 7.1 (KOH) + 1 mg/mL bacitracin) using a Ul-
- 15 tra-Turrax homogenizer for 30 seconds. The homogenate was centrifuged at 140 g in 10 min. The supernatant was transferred to a new test tube and centrifuged for 30 min at 23 000 g. Pellet was resuspended in 5-10 mL Hepes buffer, homogenized and centrifuged for 10 min at 23 000 g. This short centrifugation step is repeated twice. After the last centrifugation the pellet was resuspended in 2-4 mL Hepes buffer and
- 20 the protein concentration was determined. The membranes were diluted to a protein concentration of 5 mg/mL using Hepes buffer, aliquoted and stored at -80 °C until use
- 50 μ L test-compound, 100 μ L membrane (200 μ g/mL), 300 μ L. Hepes buffer and 50
- 25 μ L R- α -methyl[³H]histamine (1 nM) were mixed in a test tube. The compounds to be tested were dissolved in DMSO and further diluted in H₂O to the desired concentrations. Radioligand and membranes were diluted in Hepes buffer + 1 mg/mL bacitracin. The mixture was incubated for 60 min at 25 °C. Incubation was terminated by adding 5 mL ice-cold 0.9 % NaCl, followed by rapid filtration through Whatman
- 30 GF/B filters pre-treated for 1h with 0.5 % polyethyleneimine. The filters were washed with 2 x 5 mL ice-cold NaCl. To each filter a 3 mL scintillation cocktail was added and the radioactivity retained was measured with a Packard Tri-Carb beta counter.

IC₅₀ values were calculated by non-linear regression analysis of binding curves (6 points minimum) using the windows program GraphPad Prism, GraphPad software, USA.

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When tested, the present compounds of the formula (I) generally showed a high binding affinity to the histamine H3 receptor.

10

Preferably, the compounds according to the invention have an IC₅₀ value as determined by one or both of the assays of less than 1 µM, more preferred of less than 500 nM and even more preferred of less than 100 nM.

The ability of the present compounds to reduce weight was determined using the *in vivo* open cage Schedule-fed rat model.

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The open cage Schedule-fed rat model

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Sprague-Dawley (SD) male rats of an age of about 1½ to 2 months and a weight of about 250 g were habituated to the presence of food (Altromin pelleted rat chow) in their home cage only during three hours in the morning from 9 to 12 a.m. all days a week. Water was present ad libitum. As the consumption of food stabilised after 7 to 9 days, the animals were ready for use.

25

The animals were tested twice a week. During the test sessions, the test compound was administered intraperitoneally 30 minutes before the start of the sessions. One group of 9 animals was administered the test compound at a dose of 15 mg/kg and another group of 11 animals was administered the test compound at a dose of 30 mg/kg. A control group of 11 animals was administered the vehicle consisting of NaCl 0.9% and Chremophor 5%. Food and water intake were monitored at 1, 2 and 3 h post administration.

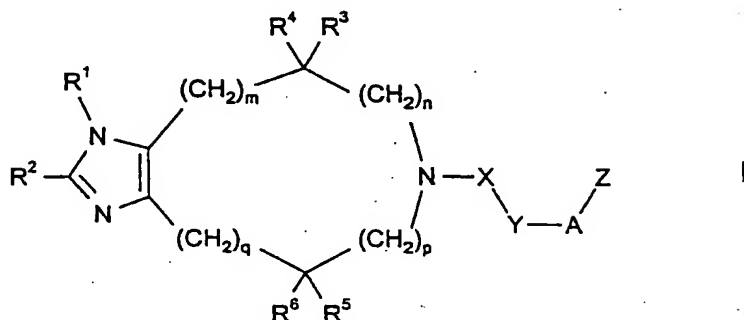
30

During the test period the animals were weighed weekly and if necessary extra food was given in order to ensure that the weight gain was 3 to 5 g per week corresponding to the normal weight gain for SD male rats at this age.

- 5 Any side effects could rapidly be discovered (barrel-rolling, bushy fur etc.) since the animals were kept in transparent plastic cages to enable continuous monitoring.

CLAIMS

1. A compound of the general formula I



wherein

R^1 is hydrogen or a functional group, which can be converted to hydrogen *in vivo*;

R^2 is hydrogen, C_{1-6} -alkyl, halogen, cyano, trifluoromethyl, trifluoromethoxy, hydroxy or $-NR^7R^8$,

wherein R^7 and R^8 independently are

hydrogen,

C_{1-6} -alkyl optionally substituted with

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroaryl-amino or C_{3-8} -cycloalkyl, which are optionally substituted with

C_{1-6} -alkyl, C_{1-6} -alkoxy, C_{1-6} -alkylthio, hydroxy, amino, C_{1-6} -alkylamino, di(C_{1-6} -alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroaryl-amino,

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl or heteroarylsulfonyl, which are optionally substituted with

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

5 C₁₋₆-alkylsulfonyl optionally substituted with

C₃₋₈-cycloalkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino, or

10

R⁷ and R⁸, together with the nitrogen atom to which they are connected, form a 3 to 8 membered, saturated or unsaturated, heterocyclic ring optionally containing one or more further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally substituted with C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

15

R³, R⁴, R⁵ and R⁶ independently are

20

hydrogen, carboxy, C₁₋₆-alkoxycarbonyl, cyano, trifluoromethyl, halogen,

C₃₋₈-cycloalkyl optionally substituted with

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino,

25

di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

C₁₋₆-alkyl, C₂₋₆-alkenyl or C₂₋₆-alkynyl, which are optionally substituted with

C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, cyano, halogen, trifluoromethyl, trifluoromethoxy, carboxy, C₁₋₆-alkoxycarbonyl,

30

C₃₋₈-cycloalkyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino, which are optionally substituted with

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroarylamino or -CO-NR⁹R¹⁰,

aryl optionally substituted with

halogen, cyano, nitro, C₁₋₆-alkyl, C₁₋₆-alkoxy, hydroxy, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aryloxy, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroarylamino or -CO-NR⁹R¹⁰,

-CO-NR⁹R¹⁰,

wherein R⁹ and R¹⁰ independently are

hydrogen,

C₁₋₆-alkyl optionally substituted with

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroarylamino or C₃₋₈-cycloalkyl, which are optionally substituted with

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl or heteroarylsulfonyl, which are optionally substituted with

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

C₁₋₆-alkylsulfonyl optionally substituted with

C₃₋₈-cycloalkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,
5 or

R⁹ and R¹⁰, together with the nitrogen atom to which they are connected, form a 3 to 8 membered, saturated or unsaturated, heterocyclic ring optionally containing one or more further heteroatoms selected from nitrogen, oxygen and sulfur,
10 and optionally substituted with C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino, or

15 R³ and R⁴, together with the carbon atom to which they are connected, and/or R⁵ and R⁶ together with the carbon atom to which they are connected, form a 3 to 8 membered, saturated or unsaturated, carbocyclic or heterocyclic ring optionally substituted with C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl,
20 aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

m, n, p and q independently are 0, 1 or 2;

X is a valence bond, -CH₂-, -C(=O)-, -C(=S)-, -S(=O)-, -S(=O)₂-, -C(=N-CN)-,
25 -C(=CH-NO₂)-, -C[=C(CN)₂]-, -C(=CH-CN)-, -C(=NR¹¹)- or -C(=N-S(=O)₂R^{11a})-,

wherein R¹¹ is

hydrogen,

30 C₁₋₆-alkyl optionally substituted with

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroarylamino or C₃₋₈-cycloalkyl, which are optionally substituted with

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl or heteroarylsulfonyl, which are optionally substituted with

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

C₁₋₆-alkylsulfonyl optionally substituted with

C₃₋₈-cycloalkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

R^{11a} is

C₁₋₆-alkyl optionally substituted with

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroarylamino or C₃₋₈-cycloalkyl, which are optionally substituted with

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl or heteroarylsulfonyl, which are optionally substituted with

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

5 Y is a valence bond, -O- or -N(R¹²)-,

wherein R¹² is

hydrogen,

10

C₁₋₆-alkyl optionally substituted with

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroarylamino or C₃₋₈-cycloalkyl, which are optionally substituted with

15

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

20 aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl or heteroarylsulfonyl, which are optionally substituted with

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

25

C₁₋₆-alkylsulfonyl optionally substituted with

C₃₋₈-cycloalkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

30

A is a valence bond, C₁₋₈-alkylene, C₂₋₈-alkenylene, C₂₋₈-alkynylene, C₃₋₈-cycloalkylene or phenylene, or

when Y is $-N(R^{12})-$, A, together with R^{12} and the nitrogen atom to which they are connected, may form a 3 to 8 membered, saturated or unsaturated, heterocyclic ring system optionally containing one or more further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally substituted with C_{1-6} -alkyl,

5 C_{1-6} -alkoxy, C_{1-6} -alkylthio, hydroxy, amino, C_{1-6} -alkylamino, di(C_{1-6} -alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aryl- C_{1-6} -alkyl, heteroaryl- C_{1-6} -alkyl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino; and

10 Z is $-R^{13}$, $-OR^{13}$, $-SR^{13}$, $-NR^{13}R^{14}$, $-CHR^{13}R^{14}$, $-CR^{13}R^{14}R^{15}$ or $=CR^{13}R^{14}$,

wherein R^{13} , R^{14} and R^{15} independently are

hydrogen,

15

C_{1-6} -alkyl, C_{2-6} -alkenyl or C_{2-6} -alkynyl, which are optionally substituted with aryl, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, C_{1-6} -alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, heteroaryl or C_{3-8} -cycloalkyl, which are optionally substituted with

20

C_{1-6} -alkyl, C_{1-6} -alkoxy, C_{1-6} -alkylthio, aryl- C_{1-6} -alkyl, heteroaryl- C_{1-6} -alkyl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6} -alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, hydroxy, amino, C_{1-6} -alkylamino, di(C_{1-6} -alkyl)amino, halogen, cyano, trifluoromethoxy or trifluoromethyl,

25

aryl, C_{3-15} -cycloalkyl, C_{3-15} -cycloalkenyl, C_{3-15} -cycloalkynyl, aroyl or heteroaryl, which are optionally substituted with

30

aryl- C_{1-6} -alkyl, heteroaryl- C_{1-6} -alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6} -alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C_{1-6} -alkyl, C_{1-6} -alkoxy, C_{1-6} -alkylthio, C_{3-8} -cycloalkanecarbonyl, hydroxy,

amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethoxy or trifluoromethyl, where

R¹³ and R¹⁴ or R¹³, R¹⁴ and R¹⁵, when they do not represent hydrogen, may be joined by one or more bridging linkers such as a valence bond, C₁₋₄-alkylene, C₂₋₄-alkenylene, -O-, -S-, -N(R¹⁶)-, -C(=O)-, -S(=O)-, -S(=O)₂-, -C(R¹⁶R¹⁷)-, phenylene, biphenylene, -O-C₁₋₄-alkylene, -S-C₁₋₄-alkylene, -N(R¹⁶)-C₁₋₄-alkylene, -N=C₁₋₄-alkylene, -O-C₂₋₄-alkenylene, -S-C₂₋₄-alkenylene or -N(R¹⁶)-C₂₋₄-alkenylene, to form a mono-, bi- or polycyclic ring system,

wherein R¹⁶ and R¹⁷ independently are

hydrogen,

C₁₋₆-alkyl optionally substituted with

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroaryl amino or C₃₋₈-cycloalkyl, which are optionally substituted with C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroaryl amino,

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl or heteroarylsulfonyl, which are optionally substituted with

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroaryl amino,

C₁₋₆-alkylsulfonyl optionally substituted with

C₃₋₈-cycloalkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoro-

methoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino, or

5 R^{16} and R^{17} , together with the nitrogen atom to which they are connected, form a 3 to 8 membered, saturated or unsaturated, heterocyclic ring optionally containing one or more further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally substituted with C_{1-6} -alkyl, C_{1-6} -alkoxy, C_{1-6} -alkylthio, hydroxy, amino, C_{1-6} -alkylamino, di(C_{1-6} -alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

with the provisos that

15 when X is -CS-, $R^1 = R^2 = R^5 = R^6 =$ hydrogen, $m = n = p = 0$ and $q = 1$, the group -Y-A-Z must not start with the radical -NH-;

when the group -X-Y-A-Z starts with the radical -CH₂-, $R^1 = R^2 = R^6 =$ hydrogen, $m = n = p = 0$ and $q = 1$, R^5 must not be carboxy or aminocarbonyl;

20 when X is -CO-, the group -Y-A-Z starts with the radical -NH-, $R^1 = R^2 = R^6 =$ hydrogen, $m = n = p = 0$ and $q = 1$, the remainder of the group -Y-A-Z must not be hydrogen, unsubstituted or C_{1-6} -alkoxy substituted phenyl, unsubstituted C_{3-8} -cycloalkyl or unsubstituted C_{1-6} -alkyl;

25 when X is -CO-, Y is -O-, A is -CH₂-, Z is phenyl, $R^1 = R^2 = R^3 = R^4 = R^6 =$ hydrogen, $m = n = p = 0$ and $q = 1$, R^5 must not be carboxy, aminocarbonyl or 4-phenyl-piperazin-1-ylcarbonyl;

30 when X is -CO-, Y is -O-, A is -CH₂-, Z is phenyl, $R^1 = R^3 = R^4 = R^6 =$ hydrogen, $R^2 =$ butyl, $m = n = p = 0$ and $q = 1$, R^5 must not be methoxycarbonyl;

when X is -CO-, Y is -O-, A is -CH₂-, Z is phenyl, R¹ = R² = R⁴ = R⁵ = R⁶ = hydrogen, m = n = p = 0 and q = 1, R³ must not be hydrogen, ethyl, isopropyl or phenyl;

5 when X is -CO-, Y is -O-, A is a valence bond, Z is *tert*-butyl, R¹ = R² = R³ = R⁴ = R⁶ = hydrogen, m = n = p = 0 and q = 1, R⁵ must not be carboxy;

when X is -CO-, Y is -O-, A is a valence bond, Z is *tert*-butyl, R¹ = R² = R⁴ = R⁵ = R⁶ = hydrogen, m = n = p = 0 and q = 1, R³ must not be 4-cyanophenyl;

10 when X is -CO-, the group -Y-A-Z starts with the radical -O-, R¹ = R² = R⁶ = hydrogen, m = n = p = 0 and q = 1, R⁵ must not be carboxy, aminocarbonyl or hydrogen;

when -X is -CO-, the group -Y-A-Z starts with the radical -CH<, R¹ = R² = R³ = R⁴ = R⁶ = hydrogen, m = n = p = 0 and q = 1, R⁵ must not be hydroxymethyl, C₁₋₆-alkoxy-
15 carbonyl or carboxy; and

when X is -CO-, the group -Y-A-Z is 4-methoxyphenyl, R¹ = R² = R³ = R⁴ = R⁶ = hydrogen, m = n = p = 0 and q = 1, R⁵ must not be carboxy;

20 as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein R¹ = R² = hydrogen.

25 3. A compound according to claim 1 or 2, wherein m = n = p = 0; and q = 1.

4. A compound according to claim 1 or 2, wherein n = p = 0; and m = q = 1.

5. A compound according to any one of the preceding claims, wherein X is a valence
30 bond, -C(=O)-, -S(=O)₂-, -C(=N-CN)-, -C(=CH-NO₂)- or -C(=N-S(=O)₂R^{11a})-, wherein R^{11a} is as defined in claim 1.

6. A compound according to claim 5, wherein X is -C(=O)-.

7. A compound according to any one of the preceding claims, wherein A is a valence bond, C₁₋₈-alkylene, C₂₋₈-alkenylene or C₂₋₈-alkynylene.

5

8. A compound according to claim 7, wherein A is a valence bond or C₁₋₈-alkylene.

9. A compound according to claim 8, wherein A is a valence bond, methylene, ethylene or propylene.

10

10. A compound according to any one of the preceding claims, wherein Z is -R¹³, -NR¹³R¹⁴, -CHR¹³R¹⁴ or -CR¹³R¹⁴R¹⁵, wherein R¹³, R¹⁴ and R¹⁵ are as defined in claim 1.

15

11. A compound according to claim 10, wherein Z is -R¹³, wherein R¹³ is as defined in claim 1.

20

12. A compound according to claim 11, wherein Z is C₁₋₆-alkyl, aryl, C₃₋₁₅-cycloalkyl, C₃₋₁₅-cycloalkenyl, aroyl or heteroaryl, which are optionally substituted as defined in claim 1.

25

13. A compound according to claim 12, wherein Z is C₁₋₆-alkyl, phenyl, naphthyl, thienyl, cyclopentyl, cyclohexyl, cyclohexenyl, oxazolyl, indanyl, isoquinolyl, benzoyl or tetrahydronaphthyl which are optionally substituted as defined in claim 1.

30

14. A compound according to claim 17, wherein Z is phenyl or cyclohexyl which are optionally substituted as defined in claim 1.

15. A compound according to any one of the preceding claims 11 to 14, wherein Z is unsubstituted or substituted with one to three substituents selected from C₁₋₆-alkyl, C₁₋₆-alkoxy, halogen, phenyl, di(C₁₋₆-alkyl)amino, C₃₋₈-cyclopropanecarbonyl, trifluoromethoxy and trifluoromethyl.

16. A compound according to claim 10, wherein Z is $-NR^{13}R^{14}$, in which R^{13} and R^{14} are both phenyl, which phenyl groups are joined with a C_{1-4} -alkylene group to form a tricyclic ring system.

5

17. A compound according to claim 10, wherein Z is $-CHR^{13}R^{14}$, in which R^{13} is C_{1-6} -alkyl or phenyl and R^{14} is phenyl, or R^{13} and R^{14} are both C_{1-6} -alkyl which are joined with C_{1-4} -alkylene linkers to form a polycarbocyclic ring system.

10

18. A compound according to claim 10, wherein Z is $-CR^{13}R^{14}R^{15}$, in which R^{13} , R^{14} and R^{15} are C_{1-6} -alkyl which are joined with C_{1-4} -alkylene linkers to form a polycarbocyclic ring system.

19. A compound according to claim 18, wherein Z is adamantyl.

15

20. A compound according to any one of the preceding claims, wherein R^3 and R^4 independently are

hydrogen;

20

C_{3-8} -cycloalkyl optionally substituted with C_{1-6} -alkyl, C_{1-6} -alkoxy, C_{1-6} -alkylthio, hydroxy, amino, C_{1-6} -alkylamino, di(C_{1-6} -alkylamino), halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

25

C_{1-6} -alkyl optionally substituted with

C_{3-8} -cycloalkyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino which are optionally substituted with

C_{1-6} -alkyl, C_{1-6} -alkoxy, C_{1-6} -alkylthio, hydroxy, amino, C_{1-6} -alkylamino,

30

di(C_{1-6} -alkylamino), halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

aryl optionally substituted with

halogen, cyano, nitro, C₁₋₆-alkyl, C₁₋₆-alkoxy, hydroxy, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aryloxy, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroarylamino or -CO-NR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined in claim 1,
5 or

R³ and R⁴, together with the carbon atom to which they are connected, form a C₃₋₈-cycloalkyl ring optionally substituted with C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkylamino), halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino.
10

21. A compound according to claim 20, wherein R³ and R⁴ are both hydrogen or are both C₁₋₆-alkyl, or R³ and R⁴, together with the carbon atom to which they are connected, form a C₃₋₈-cycloalkyl ring, or one of R³ and R⁴ is hydrogen while the other is C₃₋₈-cycloalkyl substituted C₁₋₆-alkyl.
15

22. A compound according to any one of the claims 1 to 21, wherein R⁵ and R⁶ are both hydrogen.
20

23. A compound according to any one of the claims 1 to 22, wherein R³, R⁴, R⁵ and R⁶ are hydrogen.

24. A compound according to any one of the claims 1 to 3, wherein R¹ = R² = hydrogen; R³, R⁴, R⁵ and R⁶ are hydrogen; X is -C(=O)-; Y is -N(R¹²)-, wherein R¹² and A, together with the nitrogen atom to which they are connected, form a 3 to 8 membered, saturated or unsaturated, heterocyclic ring system optionally containing one or more further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally substituted with C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkylamino), halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aryl-C₁₋₆-alkyl, heteroaryl-C₁₋₆-alkyl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino; and Z is -R¹³, wherein R¹³ is hydrogen.
25
30

25. A compound according to any one of the claims 1 to 3, wherein $R^1 = R^2 =$ hydrogen; R^3, R^4, R^5 and R^6 are hydrogen; X is $-C(=N-CN)-$, $-C(=CH-NO_2)-$ or $-C(=N-S(=O)_2R^{11a})-$, wherein R^{11a} is C_{1-6} -alkyl or phenyl substituted with C_{1-6} -alkyl; Y is $-NH-$; A is C_{1-8} -alkylene; and Z is $-R^{13}$, wherein R^{13} is C_{1-6} -alkyl, aryl, C_{3-15} -cycloalkyl, C_{3-15} -cycloalkenyl, aroyl or heteroaryl, which are optionally substituted as defined in claim 1.
- 10 26. A compound according to any one of the claims 1 to 3, wherein $R^1 = R^2 =$ hydrogen; R^3, R^4, R^5 and R^6 are hydrogen; X is $-S(=O)_2-$; Y is a valence bond; A is a valence bond or C_{1-8} -alkylene; and Z is $-R^{13}$, wherein R^{13} is C_{1-6} -alkyl, aryl, C_{3-15} -cycloalkyl, C_{3-15} -cycloalkenyl, aroyl or heteroaryl, which are optionally substituted as defined in claim 1.
- 15 27. A compound according to any one of the claims 1 to 3, wherein $R^1 = R^2 =$ hydrogen; R^3, R^4, R^5 and R^6 are hydrogen; X is $-C(=O)-$; Y is $-N(R^{12})-$, wherein R^{12} is hydrogen or C_{1-6} -alkyl; A is a valence bond or C_{1-8} -alkylene; and Z is $-R^{13}$, wherein R^{13} is C_{1-6} -alkyl, aryl, C_{3-15} -cycloalkyl, C_{3-15} -cycloalkenyl, aroyl or heteroaryl, which are optionally substituted as defined in claim 1.
- 20 28. A compound according to any one of the claims 1 to 3, wherein $R^1 = R^2 =$ hydrogen; R^3, R^4, R^5 and R^6 are hydrogen; X is $-C(=O)-$; Y is $-O-$; A is a valence bond or C_{1-8} -alkylene; and Z is $-R^{13}$, wherein R^{13} is C_{1-6} -alkyl, aryl, C_{3-15} -cycloalkyl, C_{3-15} -cycloalkenyl, aroyl or heteroaryl, which are optionally substituted as defined in claim 1.
- 25 29. A compound according to any one of the claims 1 to 3, wherein $R^1 = R^2 =$ hydrogen; R^3, R^4, R^5 and R^6 are hydrogen; X is $-C(=O)-$; Y is a valence bond; A is a valence bond or C_{1-8} -alkylene; and Z is $-R^{13}$, wherein R^{13} is C_{1-6} -alkyl, aryl, C_{3-15} -cycloalkyl, C_{3-15} -cycloalkenyl, aroyl or heteroaryl, which are optionally substituted as defined in claim 1.
- 30

30. A compound according to any one of the preceding claims 25 to 29, wherein Z is C₁₋₆-alkyl, phenyl, naphthyl, thienyl, cyclopentyl, cyclohexyl, cyclohexenyl, oxazolyl, indanyl, isoquinolyl, benzoyl or tetrahydronaphthyl which are optionally substituted as
5 defined in claim 1.

31. A compound according to claim 30, wherein Z is phenyl or cyclohexyl, which are optionally substituted as defined in claim 1.

10 32. A compound according to any one of the preceding claims 25 to 31, wherein Z is unsubstituted or substituted with one to three substituents selected from C₁₋₆-alkyl, C₁₋₆-alkoxy, halogen, phenyl, di(C₁₋₆-alkyl)amino, C₃₋₈-cyclopropanecarbonyl, trifluoromethoxy and trifluoromethyl.

15 33. A compound according to any one of the claims 1 to 32 for use as a medicament.

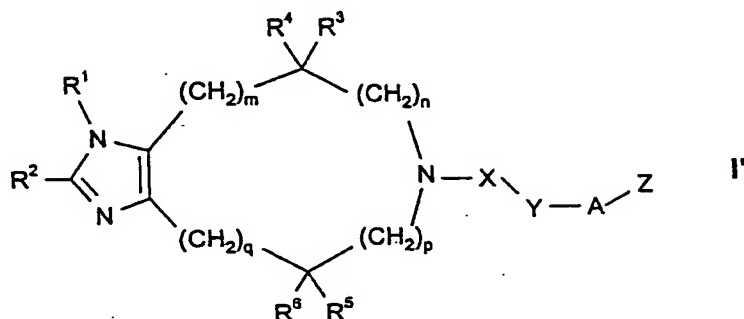
34. A pharmaceutical composition comprising, as an active ingredient, at least one compound according to any one of the claims 1 to 32 together with one or more pharmaceutically acceptable carriers or diluents.

20

35. A pharmaceutical composition according to claim 34 in unit dosage form, comprising from about 0.05 mg to about 1000 mg, preferably from about 0.1 mg to about 500 mg and especially preferred from about 0.5 mg to about 200 mg of the compound according to any one of the claims 1 to 32.

25

36. Use of a compound of the general formula I'



5 wherein

R¹ is hydrogen or a functional group, which can be converted to hydrogen *in vivo*;

R² is hydrogen, C₁₋₆-alkyl, halogen, cyano, trifluoromethyl, trifluoromethoxy, hydroxy
 10 or -NR⁷R⁸,

wherein R⁷ and R⁸ independently are

hydrogen,

15

C₁₋₆-alkyl optionally substituted with

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroaryl amino
 or C₃₋₈-cycloalkyl, which are optionally substituted with

20

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino,
 di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy,
 aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or het-
 eroaryl amino,

25

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl or heteroarylsulfonyl, which are
 optionally substituted with

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

5 C₁₋₆-alkylsulfonyl optionally substituted with

C₃₋₈-cycloalkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino, or

10

R⁷ and R⁸, together with the nitrogen atom to which they are connected, form a 3 to 8 membered, saturated or unsaturated, heterocyclic ring optionally containing one or more further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally substituted with C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

15

20

R³, R⁴, R⁵ and R⁶ independently are

hydrogen, carboxy, C₁₋₆-alkoxycarbonyl, cyano, trifluoromethyl, halogen,

C₃₋₈-cycloalkyl optionally substituted with

25

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

C₁₋₆-alkyl, C₂₋₆-alkenyl or C₂₋₆-alkynyl, which are optionally substituted with

30

C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, cyano, halogen, trifluoromethyl, trifluoromethoxy, carboxy, C₁₋₆-alkoxycarbonyl,

C₃₋₈-cycloalkyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino, which are optionally substituted with

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroarylamino or -CO-NR⁹R¹⁰,

aryl optionally substituted with

halogen, cyano, nitro, C₁₋₆-alkyl, C₁₋₆-alkoxy, hydroxy, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aryloxy, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroarylamino or -CO-NR⁹R¹⁰,

-CO-NR⁹R¹⁰,

wherein R⁹ and R¹⁰ independently are

hydrogen,

C₁₋₆-alkyl optionally substituted with

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroarylamino or C₃₋₈-cycloalkyl, which are optionally substituted with

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl or heteroarylsulfonyl, which are optionally substituted with

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

C₁₋₆-alkylsulfonyl optionally substituted with

C₃₋₈-cycloalkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino, or

R⁹ and R¹⁰, together with the nitrogen atom to which they are connected, form a 3 to 8 membered, saturated or unsaturated, heterocyclic ring optionally containing one or more further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally substituted with C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino, or

R³ and R⁴, together with the carbon atom to which they are connected, and/or R⁵ and R⁶ together with the carbon atom to which they are connected, form a 3 to 8 membered, saturated or unsaturated, carbocyclic or heterocyclic ring optionally substituted with C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

m, n, p and q independently are 0, 1 or 2;

X is a valence bond, -CH₂-, -C(=O)-, -C(=S)-, -S(=O)-, -S(=O)₂-, -C(=N-CN)-, -C(=CH-NO₂)-, -C[=C(CN)₂]-, -C(=CH-CN)-, -C(=NR¹¹)- or -C(=N-S(=O)₂R^{11a})-,

wherein R¹¹ is

hydrogen,

C₁₋₆-alkyl optionally substituted with

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroarylamino or C₃₋₈-cycloalkyl, which are optionally substituted with

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl or heteroarylsulfonyl, which are optionally substituted with

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

C₁₋₆-alkylsulfonyl optionally substituted with

C₃₋₈-cycloalkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

R^{11a} is

C₁₋₆-alkyl optionally substituted with

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroarylamino or C₃₋₈-cycloalkyl, which are optionally substituted with

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl or heteroarylsulfonyl, which are optionally substituted with

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

5 Y is a valence bond, -O- or -N(R¹²)-,

wherein R¹² is

hydrogen,

10

C₁₋₆-alkyl optionally substituted with

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroarylamino or C₃₋₈-cycloalkyl, which are optionally substituted with

15

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl or heteroarylsulfonyl, which are optionally substituted with

20

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino,

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C₁₋₆-alkylsulfonyl optionally substituted with

C₃₋₈-cycloalkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

30

A is a valence bond, C₁₋₈-alkylene, C₂₋₈-alkenylene, C₂₋₈-alkynylene, C₃₋₈-cycloalkylene or phenylene, or

when Y is -N(R¹²)-, A, together with R¹² and the nitrogen atom to which they are connected, may form a 3 to 8 membered, saturated or unsaturated, heterocyclic ring system optionally containing one or more further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally substituted with C₁₋₆-alkyl,

C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aryl-C₁₋₆-alkyl, heteroaryl-C₁₋₆-alkyl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroaryl-amino; and

Z is -R¹³, -OR¹³, -SR¹³, -NR¹³R¹⁴, -CHR¹³R¹⁴, -CR¹³R¹⁴R¹⁵ or =CR¹³R¹⁴,

wherein R¹³, R¹⁴ and R¹⁵ independently are

hydrogen,

C₁₋₆-alkyl, C₂₋₆-alkenyl or C₂₋₆-alkynyl, which are optionally substituted with aryl, arylamino, heteroaryl-amino, aroyl, heteroaroyl, arylsulfonyl, C₁₋₆-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, heteroaryl or C₃₋₈-cycloalkyl, which are optionally substituted with

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, aryl-C₁₋₆-alkyl, heteroaryl-C₁₋₆-alkyl, nitro, arylamino, heteroaryl-amino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C₁₋₆-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethoxy or trifluoromethyl,

aryl, C₃₋₁₅-cycloalkyl, C₃₋₁₅-cycloalkenyl, C₃₋₁₅-cycloalkynyl, aroyl or heteroaryl, which are optionally substituted with

aryl-C₁₋₆-alkyl, heteroaryl-C₁₋₆-alkyl, aryl, heteroaryl, nitro, arylamino, heteroaryl-amino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C₁₋₆-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, C₃₋₈-cycloalkanecarbonyl, hydroxy,

amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethoxy or trifluoromethyl, where

R¹³ and R¹⁴ or R¹³, R¹⁴ and R¹⁵, when they do not represent hydrogen, may be joined by one or more bridging linkers such as a valence bond, C₁₋₄-alkylene, C₂₋₄-alkenylene, -O-, -S-, -N(R¹⁶)-, -C(=O)-, -S(=O)-, -S(=O)₂-, -C(R¹⁶R¹⁷)-, phenylene, biphenylene, -O-C₁₋₄-alkylene, -S-C₁₋₄-alkylene, -N(R¹⁶)-C₁₋₄-alkylene, -N=C₁₋₄-alkylene, -O-C₂₋₄-alkenylene, -S-C₂₋₄-alkenylene or -N(R¹⁶)-C₂₋₄-alkenylene, to form a mono-, bi- or polycyclic ring system,

wherein R¹⁶ and R¹⁷ independently are

hydrogen,

C₁₋₆-alkyl optionally substituted with

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroaryl amino or C₃₋₈-cycloalkyl, which are optionally substituted with C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroaryl amino,

aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl or heteroarylsulfonyl, which are optionally substituted with

C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroaryl amino,

C₁₋₆-alkylsulfonyl optionally substituted with

C₃₋₈-cycloalkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoro-

methoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino, or

5 R¹⁶ and R¹⁷, together with the nitrogen atom to which they are connected, form a 3 to 8 membered, saturated or unsaturated, heterocyclic ring optionally containing one or more further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally substituted with C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, C₁₋₆-alkylamino, di(C₁₋₆-alkyl)amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

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as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof for the preparation of a medicament for the treatment and/or prevention of disorders and diseases related to the histamine H3 receptor.

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37. Use of a compound as defined in claim 36 for the preparation of a medicament for the treatment and/or prevention of disorders and diseases, in which an inhibition of the histamine H3 receptor has a beneficial effect.

20 38. Use of a compound as defined in claim 36 for the preparation of a medicament having H3 antagonistic action.

39. Use of a compound as defined in claim 36 for the preparation of a pharmaceutical composition for the reduction of weight.

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40. Use of a compound as defined in claim 36 for the preparation of a pharmaceutical composition for the treatment and/or prevention of overweight or obesity.

30 41. Use of a compound as defined in claim 36 for the preparation of a pharmaceutical composition for the suppression of appetite or satiety induction.

42. Use of a compound as defined in claim 36 for the preparation of a pharmaceutical composition for the prevention and/or treatment of disorders and diseases related to overweight or obesity.
- 5 43. Use of a compound as defined in claim 36 for the preparation of a pharmaceutical composition for the prevention and/or treatment of eating disorders such as bulimia and binge eating.
44. Use of a compound as defined in claim 36 for the preparation of a pharmaceutical composition for the treatment and/or prevention of IGT.
- 10 45. Use of a compound as defined in claim 36 for the preparation of a pharmaceutical composition for the treatment and/or prevention of Type 2 diabetes.
- 15 46. Use of a compound as defined in claim 36 for the preparation of a pharmaceutical composition for the delaying or prevention of the progression from IGT to Type 2 diabetes.
47. Use of a compound as defined in claim 36 for the preparation of a pharmaceutical composition for the delaying or prevention of the progression from non-insulin requiring Type 2 diabetes to insulin requiring Type 2 diabetes.
- 20 48. Use of a compound as defined in claim 36 for the preparation of a pharmaceutical composition for the treatment and/or prevention of diseases and disorders related to the serotonin-3 receptor (5-HT₃), such as for use in the treatment of emesis.
- 25 49. Use of a compound as defined in claim 36 for the preparation of a pharmaceutical composition for the treatment and/or prevention of diseases and disorders related to the vanilloid receptor, such as for use in the treatment of pain, neurogenic inflammation or obesity.
- 30

50. Use of a compound as defined in claim 36 for the preparation of a pharmaceutical composition for the treatment and/or prevention of diseases and disorders related to the alpha-2 adrenergic receptor, such as for use as a sleep inducing agent.

- 5 51. A method for the treatment and/or prevention of disorders or diseases related to the H3 histamine receptor the method comprising administering to a subject in need thereof an effective amount of a compound according to claim 36 or a pharmaceutical composition comprising the same.
- 10 52. The method according to claim 51, wherein the effective amount of the compound is in the range of from about 0.05 mg to about 2000 mg; preferably from about 0.1 mg to about 1000 mg and especially preferred from about 0.5 mg to about 500 mg per day.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 00/00179

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 471/04, C07D 487/04, A61K 31/437, A61K 31/4188

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J.MED.CHEM., Volume 38, 1995, Michael Krause et al, "Synthesis, X-ray Crystallography, and Pharmacokinetics of Novel Azomethine Prodrugs of (R)-alfa-Methylhistamine: Highly Potent and Selective Histamine H3 Receptor Agonists", page 4070 - page 4079, compound 11 -- -----	



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

8 August 2000

Date of mailing of the international search report

14-08-2000

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK00/00179

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 51-52
because they relate to subject matter not required to be searched by this Authority, namely:
**A method for treatment of the human or animal body by therapy,
see rule 39.1.**
2. ☒ Claims Nos.: 1-50
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
See extra sheet.
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK00/00179

The formulation of claims 1-35 is so complicated, owing to the very wide range of combinations of variable parts and disclaimer parts, that PCT Article 6 is no longer complied with. A meaningful search of these claims has not been possible to perform.

Claims 36 relate to the use of an extremely large number of possible compounds. The use given in claims 36-38 "treatment and/or prevention of disorders and diseases related to the histamine H3 receptor" and a similar expression in claim 37 are not considered clear and concise. Further, claims 39-50 relate to the use of the compounds according to claim 36 for a great number of diseases and conditions. It is not clear from claims 39-50 whether or not the pharmaceutical activity is related to the histamine H3 receptor.

Due to the complex drafting of claims 36-50, the search performed concerns documents which contain explicit information of histamine H3 activity of compounds according to the examples.

The applicants attention is drawn to the fact that claims relating to inventions in which no international search report has been established will not be the subject of an international preliminary examination (Rule 66.1(e) PCT). This is the case irrespective of whether or not the claims are amended following receipt of the search report during any Chapter II procedure.

App. No. 10/763,877
Filed: January 23, 2004
Inventor: DEFOSSA, et. al.
Docket No. DEAV2003/0004 US NP
PRIOR ART